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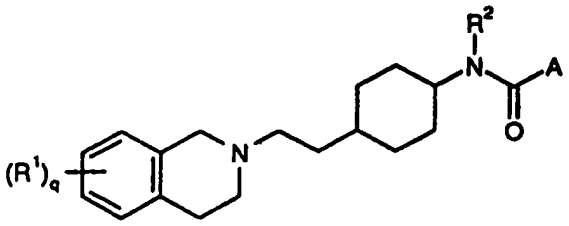
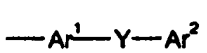
(54) Title: TETRAHYDROISOQUINOLINE DERIVATIVES AS MODULATORS OF DOPAMINE D_3 RECEPTORS



(I)

(a)



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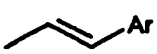

(c)

(57) Abstract

Compounds of formula (I) wherein: R represents a substituent selected from: a hydrogen or a substituent as defined in the claims; R^2 represents a hydrogen atom or a C_{1-4}alkyl group; q is 1 or 2; A represents a group of formula (a), (b) or (c) wherein: Ar represents an optionally substituted phenyl ring or an optionally substituted 5– or 6–membered aromatic heterocyclic ring; or an optionally substituted bicyclic ring system; Ar^1 and Ar^2 each independently represent an optionally substituted phenyl ring or an optionally substituted 5– or 6–membered aromatic heterocyclic ring; and Y represents a bond, –NHCO–, –CONH–, $–CH_2–$, or $–(CH_2)_mY^1(CH_2)_n–$, wherein Y^1 represents O, S, SO_2, or CO and m and n each represent zero or 1 such that the sum of m+n is zero or 1; providing that when A represents a group of formula (a), any substituent present in Ar *ortho* to the carboxamide moiety is necessarily a hydrogen or a methoxy group; and salts thereof. Compounds of formula (I) and their salts have affinity for dopamine receptors, in particular the D_3 receptor, and thus potential in the treatment of conditions wherein modulation of the D_3 receptor is beneficial, e.g. as antipsychotic agents.

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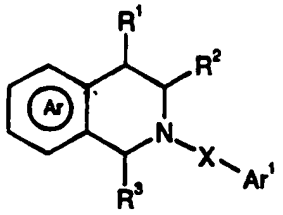
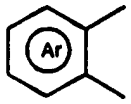
TETRAHYDROISOQUINOLINE DERIVATIVES AS MODULATORS OF DOPAMINE D3 RECEPTORS

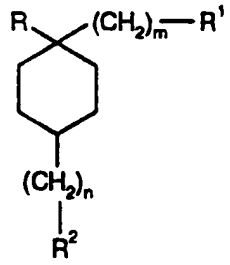
The present invention relates to novel tetrahydroisoquinoline derivatives, processes for their preparation, pharmaceutical compositions containing them and their use in therapy, as modulators of dopamine D_3 receptors, in particular as antipsychotic agents.

US Patent No. 5,294,621 describes tetrahydropyridine derivatives of the formula:

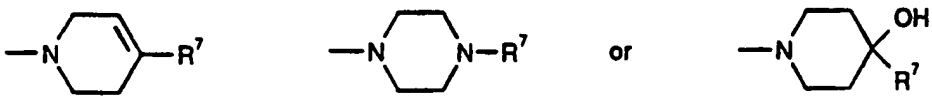


wherein  is an optionally substituted thienyl or optionally substituted phenyl ring; R^1, R^2 and R^3 are each *inter alia* hydrogen; X is *inter alia* $(CH_2)mNR^7CO$; m is 2-4; and Ar^1 is an optionally substituted heterocyclic ring or an optionally substituted phenyl ring. The compounds are said to be useful as antiarrhythmic agents.

EPA 431,580 describes compounds of formula



wherein R is OR^3, NR^4R^5, or $N(OR^4)R^5$, R^4 and R^5 are *inter alia* hydrogen, lower alkyl, aroyl or heteroaroyl; m is zero, 1 or 2; R^1 is hydrogen, aryl or various heteroaryl groups; n is zero or 1-4; and R^2 is:

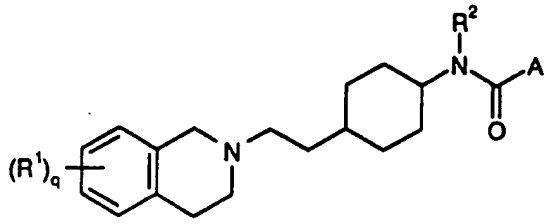


The compounds are said to be dopaminergic agents useful as antipsychotics, antihypertensives and also of use in the treatment of hyperprolactinaemia-related conditions and several central nervous system disorders.

WO 95/10513 describes benzothiophene derivatives and related compounds as estrogen agonists.

We have now found a class of tetrahydroisoquinoline derivatives which have affinity for dopamine receptors, in particular the D_3 receptor, and thus potential in the treatment of conditions wherein modulation of the D_3 receptor is beneficial, eg as antipsychotic agents.

In a first aspect the present invention provides compounds of formula (I) :



Formula (I)

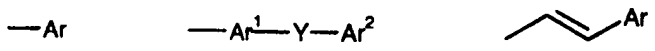
wherein:

R^1 represents a substituent selected from: a hydrogen or halogen atom; a hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethanesulfonyloxy, pentafluoroethyl, C_{1-4}alkyl, C_{1-4}alkoxy, arylC_{1-4}alkoxy, C_{1-4}alkylthio, C_{1-4}alkoxyC_{1-4}alkyl, C_{3-6}cycloalkylC_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkoxycarbonyl, C_{1-4}alkylsulfonyl, C_{1-4}alkylsulfonyloxy, C_{1-4}alkylsulfonylC_{1-4}alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-4}alkyl, C_{1-4}alkylsulfonamido, C_{1-4}alkylamido, C_{1-4}alkylsulfonamidoC_{1-4}alkyl, C_{1-4}alkylamidoC_{1-4}alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-4}alkyl, arylcarboxamidoC_{1-4}alkyl, aroyl, aroylC_{1-4}alkyl, or arylC_{1-4}alkanoyl group; a group $R^3OCO(CH_2)_p$, $R^3CON(R^4)(CH_2)_p$, $R^3R^4NCO(CH_2)_p$ or $R^3R^4NSO_2(CH_2)_p$ where each of R^3 and R^4 independently represents a hydrogen atom or a C_{1-4}alkyl group or R^3R^4 forms part of a C_{3-6}azacyloalkane or C_{3-6}(2-oxo)azacycloalkane ring and p represents zero or an integer from 1 to 4; or a group Ar^3-Z, wherein Ar^3 represents an optionally substituted phenyl ring or an optionally substituted 5- or 6- membered aromatic heterocyclic ring and Z represents a bond, O, S , or CH_2;

R^2 represents a hydrogen atom or a C_{1-4}alkyl group;

q is 1 or 2;

A represents a group of the formula (a), (b) or (c):



(a) (b) (c)

wherein

Ar represents an optionally substituted phenyl ring or an optionally substituted 5- or 6- membered aromatic heterocyclic ring; or an optionally substituted bicyclic ring system;

Ar^1 and Ar^2 each independently represent an optionally substituted phenyl ring or an optionally substituted 5- or 6- membered aromatic heterocyclic ring; and

Y represents a bond, -NHCO-, -CONH-, $-CH_2-$, or $-(CH_2)_mY^1(CH_2)_n-$, wherein Y^1 represents O, S, SO_2, or CO and m and n each represent zero or 1 such that the sum of m+n is zero or 1; providing that when A represents a group of formula (a), any substituent present in Ar *ortho* to the carboxamide moiety is necessarily a hydrogen or a methoxy group;

and salts thereof.

In the compounds of formula (I) above an alkyl group or moiety may be straight or branched. Alkyl groups which may be employed include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl and any branched isomers thereof such as isopropyl, t-butyl, sec-butyl, and the like.

Examples of compounds of formula (I) include those in which Ar is a bicyclic aromatic or heteroaromatic ring system and in which R^1 is other than pentafluoroethyl.

When R^1 represents an arylC_{1-4}alkoxy, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-4}alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-4}alkyl, arylcarboxamidoC_{1-4}alkyl, aroyl, aroylC_{1-4}alkyl, or arylC_{1-4}alkanoyl group, the aryl moiety may be selected from an optionally substituted phenyl ring or an optionally substituted 5- or 6-membered heterocyclic ring. In the group R^1 an aryl moiety may be optionally substituted by one or more substituents selected from hydrogen, halogen, amino, cyano, C_{1-4}alkyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, C_{1-4}alkylamido, C_{1-4}alkanoyl, or R^5R^6NCO where each of R^5 and R^6 independently represents a hydrogen atom or C_{1-4}alkyl group.

A halogen atom present in the compounds of formula (I) may be fluorine, chlorine, bromine or iodine.

When q is 2, the substituents R^1 may be the same or different.

An optionally substituted 5- or 6-membered heterocyclic aromatic ring, as defined for any of the groups Ar, Ar^1, Ar^2 or Ar^3 may contain from 1 to 4 heteroatoms selected from O, N or S. When the ring contains 2-4 heteroatoms, one is preferably selected from O, N and S and the remaining heteroatoms are preferably N. Examples of 5 and 6-membered heterocyclic groups include furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazyl, pyrimidinyl and pyrazolyl.

Examples of bicyclic, for example bicyclic aromatic or heteroaromatic, ring systems for Ar include naphthyl, indazolyl, indolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzisothiazolyl, quinolinyl, quinoxolinyl, quinazolinyl, cinnolinyl, isoquinolinyl, pyrazolo[1,5-a]pyrimidyl, pyrrolo[3,2-b]pyridyl, pyrrolo[3,2-c]pyridyl, thieno[3,2-b]thiophenyl, 1,2-dihydro-2-oxo-quinolinyl, 2,3-dihydro-3-oxo-4*H*-benzoxazinyl, 1,2-dihydro-2-oxo-3H-indolyl.

The rings Ar, Ar^1, or Ar^2 may each independently be optionally substituted by one or more substituents selected from: a hydrogen or halogen atom, or a hydroxy, oxo, cyano, nitro, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylenedioxy, C_{1-4}alkanoyl, C_{1-4}alkylsulfonyl, C_{1-4}alkylsulfinyl, C_{1-4}alkylthio, $R^7SO_2N(R^8)-$, $R^7R^8NSO_2-$,

R^7R^8N-, R^7R^8NCO-, or $R^7CON(R^8)$- group wherein each of R^7 and R^8 independently represents a hydrogen atom or a C_{1-4} alkyl group, or R^7R^8 together form a C_{3-6} alkylene chain.

Alternatively, Ar and Ar^2 may be optionally substituted by one or more 5- or 6-membered heterocyclic rings, as defined above, optionally substituted by a C_{1-2} alkyl or R^7R^8N- group; wherein R^7 and R^8 are as defined above.

In the rings Ar and Ar^2 substituents positioned *ortho* to one another may be linked to form a 5- or 6- membered ring.

It will be appreciated that for use in medicine the salts of formula (I) should be physiologically acceptable. Suitable physiologically acceptable salts will be apparent to those skilled in the art and include for example acid addition salts formed with inorganic acids eg. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids eg. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Other non-physiologically acceptable salts eg. oxalates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates of compounds of formula (I).

Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

The compounds of formula (I) can exist in the form of *cis*- and *trans*- isomers with respect to the configuration at the cyclohexyl ring. When A represents a group (c) the compounds may also exist as geometric isomers around the double bond. The present invention includes within its scope all such isomers, including mixtures. Preferably the compounds of the invention are in the *trans* configuration with respect to the cyclohexyl ring. For compounds of formula (I) where A represents a group (c), *trans* geometry of the double bond is preferred.

In compounds of formula (I), it is preferred that R^1 represents a substituent selected from: a halogen atom, methyl, cyano, trifluoromethyl, pentafluoroethyl, or trifluoromethoxy group. A cyano group, for example in the 6- or 7-position of the tetrahydroisoquinoline ring, is especially preferred. Preferably q is 1. R^2 is preferably a hydrogen atom.

The group A is preferably a group of formula (a) or (c). With regard to (a), preferred examples of Ar include optionally substituted indolyl, pyrazolo[1,5-a]pyrimidyl, cinnolinyl, quinolinyl, benzo[b]furanyl or pyrrolopyridyl. With regard to (c), preferred examples are optionally substituted phenyl groups.

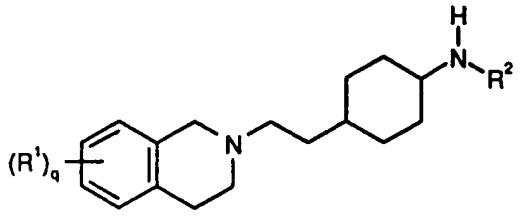
It is also preferred that the rings Ar, Ar^1, or Ar^2 are each independently optionally substituted by one or more substituents selected from: a hydrogen or halogen atom, cyano, methoxy, methylenedioxy, acetyl, acetylamino, methylsulfonyl, methylsulfonyloxy, methylaminosulfonyl, methylsulfonylamino, or methylaminocarbonyl group.

Certain of the substituted heteroaromatic ring systems included in compounds of formula (I) may exist in one or more tautomeric forms. The present invention includes within its scope all such tautomeric forms, including mixtures.

Particular compounds according to the invention include those specifically exemplified and named hereinafter. Preferred compounds according to the present invention include the first-mentioned compounds in each of Examples 1-33, the compound of Example 19, namely ***trans***-6-cyano-2-(2-(1-(4-(4-quinolinyl)-carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline, being especially preferred. These compounds may be in the form of their free base or physiologically acceptable salts thereof, particularly the monohydrochloride or monomesylate salts.

The present invention also provides a process for preparing compounds of formula (I) which process comprises :

(a) reacting a compound of formula (II):



Formula (II)

wherein R^1, R^2 and q are as hereinbefore defined, with a compound of formula (III):

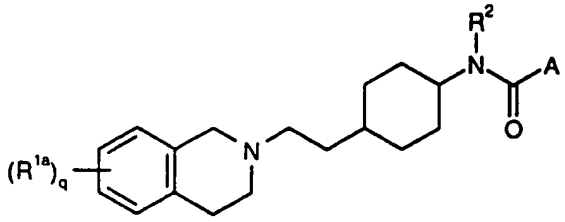
A-COX

Formula (III)

wherein A is as hereinbefore defined and X is a halogen atom or the residue of an activated ester;

(b) to prepare a compound of formula (I) by reacting a compound of formula (II) with a compound A-Br, or A-I, or A-OSO_2CF_3 in the presence of carbon monoxide and a catalyst such as *trans-bis*-triphenylphosphinepalladium(II)bromide;

(c) to prepare a compound of formula (I) wherein R^1 is Ar^3-Z and Z is a bond, reacting a compound of formula (IV):

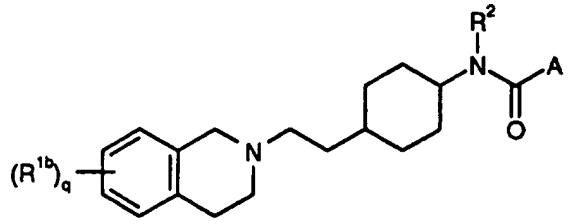


Formula (IV)

wherein R^2 and A are as hereinbefore defined and one R^{1a} represents a group W wherein W is a halogen atom or a trifluoromethylsulfonyloxy group, or W is a group M selected from a boron derivative e.g. a boronic acid function $B(OH)_2$ or a metal function such as

trialkylstannyl e.g. $SnBu_3$, zinc halide or magnesium halide, and when q is 2 the other R^{1a} is R^1; with a compound Ar^3-W^1, wherein W^1 is a halogen atom or a trifluoromethylsulfonyloxy group when W is a group M or W^1 is a group M when W is a halogen atom or a trifluoromethylsulfonyloxy group;

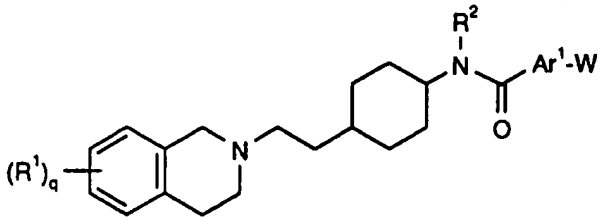
(d) to prepare a compound of formula (I) wherein R^1 is Ar^3-Z and Z is O or S, reacting a compound of formula (V):



Formula (V)

wherein R^2 and A are as hereinbefore defined and one R^{1b} represents a group ZH and when q is 2 the other R^{1b} represents R^1; with a reagent serving to introduce the group Ar^3;

(e) to prepare a compound of formula (I) where Y is a bond, reaction of a compound of formula (VI):



Formula (VI)

wherein R^1, R^2, Ar^1, W and q are as hereinbefore defined, with a compound Ar^2-W^1, wherein W^1 is a halogen atom or a trifluoromethylsulfonyloxy group when W is a group M, or W^1 is a group M when W is a halogen atom or a trifluoromethylsulfonyloxy group.

(f) interconversion of one compound of formula (I) to a different compound of formula (I) e.g. (i) alkylation of a compound (I) wherein R^2 represents hydrogen, (ii) conversion of one R^1 from alkoxy (e.g.methoxy) to hydroxy, or (iii) conversion of R^1 from hydroxy to sulfonyloxy, eg alkylsulfonyloxy or trifluoromethanesulfonyloxy; (iv) conversion of a compound wherein Y represents S to a compound wherein Y is SO_2 or (v) conversion of Y from CO to CH_2;

(g) separation of *cis*- and *trans*- isomers of compounds of formula (I) by conventional methods, e.g. chromatography or crystallisation;

and optionally thereafter forming a salt of formula (I).

Process (a) may be effected using conventional methods for the formation of an amide bond. When X is the residue of an activated ester this may be formed with e.g. a

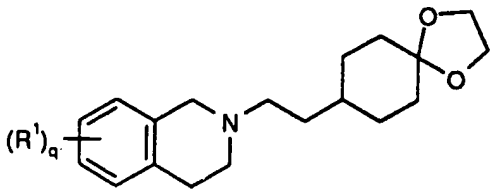
carbodiimide such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. The reaction may be carried out in a solvent such as dichloromethane.

Reaction of a compound of formula (IV) with Ar^3W^1, according to process (c) or a compound of formula (VI) with Ar^2-W^1 according to process (e) may be effected in the presence of a transition metal eg palladium catalyst such as *bis*-triphenylphosphinepalladium dichloride or *tetrakis*-triphenylphosphinepalladium (0). When M represents a boronic acid function such as $B(OH)_2$the reaction may be carried out under basic conditions, for example using aqueous sodium carbonate in a suitable solvent such as dioxane. When M is trialkylstannyl the reaction may be carried out in an inert solvent, such as xylene or dioxane optionally in the presence of LiCl. When M is a zinc or magnesium halide the reaction may be effected in an aprotic solvent such as tetrahydrofuran. The substituent W is preferably a halogen atom such as bromine, or a sulfonyloxy group such as trifluoromethylsulfonyloxy; and W^1 is preferably a goup M, such as trialkylstannyl or $B(OH)_2$.

In process (d) the reagent serving to introduce the group Ar^3 is preferably a compound of formula Ar^3-Hal, wherein Hal is a halogen atom. The reaction may be effected in the presence of a base, such as potassium carbonate, in a solvent such as dimethylformamide.

Interconversion reactions according to process (f) may be effected using methods well known in the art.

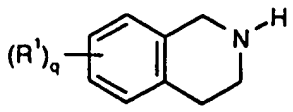
Compounds of formula (II) may be prepared by conversion of a compound of formula (VII), wherein R^1 and q are as hereinbefore defined,



Formula (VII)

into a corresponding ketone, followed by reductive amination. This may be effected by methods well known in the art for (i) conversion of a ketal to a ketone in the presence of aqueous acid; followed by (ii) reductive amination of the ketone with R^2NH_2 or ammonium acetate in the presence of a reducing agent. Suitable reducing agents which may be employed include sodium borohydride, cyanoborohydride or triacetoxyborohydride under acidic conditions, or catalytic hydrogenation. The reaction may conveniently be effected in a solvent such as methanol, ethanol or dichloroethane.

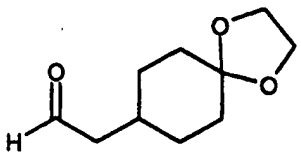
A compound of formula (VII) may itself be prepared by reacting a compound of formula (VIII):



Formula (VIII)

wherein R^1 and q are as hereinbefore defined;

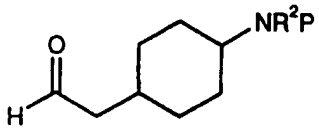
with a compound of formula (IX):



Formula (IX)

in the presence of a reducing agent. Suitable reducing agents which may be employed include sodium borohydride, cyanoborohydride or triacetoxyborohydride under acidic conditions, or catalytic hydrogenation. The reaction may conveniently be effected in a solvent such as ethanol or dichloroethane.

The individual *cis-* and *trans-* isomers of a compound of formula (II) may be prepared starting from *cis-* or *trans-* 4-amino-cyclohexaneacetic acid (T.P. Johnson, *et al.*, J. Med. Chem., 1997, (20), 279-290) followed by functional group interchange and/or protection using methods well known in the art, to give the individual *cis-* or *trans-* isomers of a compound of formula (X):



Formula (X)

wherein R^2 is as hereinbefore defined, and P is a protecting group, for example trifluoroacetyl or *tert*-butoxycarbonyl. Subsequent reaction of a compound of formula (X) with a compound of formula (VIII) in the presence of a reducing agent as described above followed by deprotection using standard methodology gives the individual isomers of a compound of formula (II) wherein R^2 is as hereinbefore defined.

Compounds of formula (III) are known or may be prepared using standard procedures.

Compounds of formula (IV), (V) or (VI) may be prepared by processes analogous to (a), (b), (c) and (d) described above. Compounds Ar^2W^1, Ar^3W^1 and Ar^3Hal are commercially available or may be prepared by standard methods. Compounds of formula (VIII) are known in the literature or may be prepared by known methods. The compound of formula (IX) is likewise known in the literature.

Compounds of formula (I) have been found to exhibit affinity for dopamine receptors, in particular the D_3 receptor, and are expected to be useful in the treatment of disease states which require modulation of such receptors, such as psychotic conditions. Compounds of formula (I) have also been found to have greater affinity for dopamine D_3

than for D_2 receptors. The therapeutic effect of currently available antipsychotic agents (neuroleptics) is generally believed to be exerted via blockade of D_2 receptors; however this mechanism is also thought to be responsible for undesirable extrapyramidal side effects (eps) associated with many neuroleptic agents. Without wishing to be bound by theory, it has been suggested that blockade of the recently characterised dopamine D_3 receptor may give rise to beneficial antipsychotic activity without significant eps. (see for example Sokoloff et al, Nature, 1990; 347: 146-151; and Schwartz et al, Clinical Neuropharmacology, Vol 16, No. 4, 295-314, 1993). Preferred compounds of the present invention are therefore those which have higher affinity for dopamine D_3 than dopamine D_2 receptors (such affinity can be measured using standard methodology for example using cloned dopamine receptors). Said compounds may advantageously be used as selective modulators of D_3 receptors.

We have found that certain compounds of formula (I) are dopamine D_3 receptor antagonists, others may be agonists or partial agonists. The functional activity of compounds of the invention (i.e. whether they are antagonists, agonists or partial agonists) can be readily determined using the test method described hereinafter, which does not require undue experimentation. D_3 antagonists are of potential use as antipsychotic agents for example in the treatment of schizophrenia, schizo-affective disorders, psychotic depression, mania, paranoid and delusional disorders. Conditions which may be treated by dopamine D_3 receptor agonists include dyskinetic disorders such as Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias; depression; anxiety, memory disorders, sexual dysfunction and drug (eg. cocaine) dependency.

In a further aspect therefore the present invention provides a method of treating conditions which require modulation of dopamine D_3 receptors, for example psychoses such as schizophrenia, which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) or a physiologically acceptable salt thereof.

The invention also provides the use of a compound of formula (I) or a physiologically acceptable salt thereof in the manufacture of a medicament for the treatment of conditions which require modulation of dopamine D_3 receptors, for example psychoses such as schizophrenia.

A preferred use for D_3 antagonists according to the present invention is in the treatment of psychoses such as schizophrenia.

A preferred use for D_3 agonists according to the present invention is in the treatment of dyskinetic disorders such as Parkinson's disease.

For use in medicine, the compounds of the present invention are usually administered as a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising a novel compound of formula (I) or a physiologically acceptable salt thereof and a physiologically acceptable carrier.

The compounds of formula (I) may be administered by any convenient method, for example by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

The compounds of formula (I) and their physiologically acceptable salts which are active when given orally can be formulated as liquids or solids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or physiologically acceptable salt in a suitable liquid carrier(s) for example an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or physiologically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as a fluoro-chlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I) or a physiologically acceptable salt thereof calculated as the free base.

The physiologically acceptable compounds of the invention will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of between 1 mg and 500 mg, preferably between 10 mg and 400 mg,e.g. between 10 and 250 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 50 mg, e.g. between 1 and 25 mg of the compound of the formula (I) or a physiologically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

Biological Test Methods

The ability of the compounds to bind selectively to human D_3 dopamine receptors can be demonstrated by measuring their binding to cloned receptors. The inhibition constants (K_i) of test compounds for displacement of [^{125}I] iodosulpride binding to human D_3 dopamine receptors expressed in CHO cells were determined as follows. The cell lines were shown to be free from bacterial, fungal and mycoplasmal contaminants, and stocks of each were stored frozen in liquid nitrogen. Cultures were grown as monolayers or in suspension in standard cell culture media. Cells were recovered by scraping (from monolayers) or by centrifugation (from suspension cultures), and were washed two or three times by suspension in phosphate buffered saline followed by collection by centrifugation. Cell pellets were stored frozen at -40°C. Crude cell membranes were prepared by homogenisation followed by high-speed centrifugation, and characterisation of cloned receptors achieved by radioligand binding.

Preparation of CHO cell membranes

Cell pellets were gently thawed at room temperature, and resuspended in about 20 volumes of ice-cold 50 mM Tris salts (pH 7.4 @ 37°C), 20mM EDTA, 0.2 M sucrose. The suspension was homogenised using an Ultra-Turrax at full speed for 15 sec. The homogenate was centrifuged at 18,000 r.p.m for 20 min at 4°C in a Sorvall RC5C centrifuge. The membrane pellet was resuspended in ice-cold 50 mM Tris salts (pH 7.4 @ 37°C), using an Ultra-Turrax, and recentrifuged at 18,000 r.p.m for 15 min at 4°C in a Sorvall RC5C. The membranes were washed two more times with ice-cold 50 mM Tris salts (pH 7.4 @ 37°C). The final pellet was resuspended in 50 mM Tris salts (pH 7.4 @ 37°C), and the protein content determined using bovine serum albumin as a standard (Bradford, M. M. (1976) Anal. Biochem. 72, 248-254).

Binding experiments on cloned dopamine receptors

Crude cell membranes were incubated with 0.1 nM [^{125}I] iodosulpride (~2000 Ci/mmol; Amersham, U. K.), and the test compound in a buffer containing 50 mM Tris salts (pH 7.4 @ 37°C), 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 0.1% (w/v) bovine

serum albumin, in a total volume of 1 ml for 30 min at 37°C. Following incubation, samples were filtered using a Brandel Cell Harvester, and washed three times with ice-cold 50 mM Tris salts (pH 7.4 @ 37°C), 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$. The radioactivity on the filters was measured using a Cobra gamma counter (Canberra Packard). Non-specific binding was defined as the radioligand binding remaining after incubation in the presence of 100 µM iodosulpride. For competition curves, 14 concentrations (half-log dilutions) of competing cold drug were used. Competition curves were analysed simultaneously whenever possible using non-linear least-squares fitting procedures, capable of fitting one, two or three site models.

Compounds of Examples tested according to this method had pKi values in the range 7.0 - 9.1 at the human cloned dopamine D_3 receptor.

Functional Activity at cloned dopamine receptors

The functional activity of compounds at human D2 and human D3 receptors (ie agonism or antagonism) may be determined using a Cytosensor Microphysiometer (McConnell HM et al Science 1992 257 1906-1912) In Microphysiometer experiments, cells (hD2_CHO or hD3_CHO) were seeded into 12mm Transwell inserts (Costar) at 300000 cells/cup in foetal calf serum (FCS)-containing medium. The cells were incubated for 6h at 37°C in 5%CO_2, before changing to FCS-free medium. After a further 16-18h, cups were loaded into the sensor chambers of the Cytosensor Microphysiometer (Molecular Devices) and the chambers perfused with running medium (bicarbonate-free Dulbecco's modified Eagles medium containing 2 mM glutamine and 44 mM NaCl) at a flow rate of 100 ul/min. Each pump cycle lasted 90s. The pump was on for the first 60s and the acidification rate determined between 68 and 88s, using the Cytosoft programme. Test compounds were diluted in running medium. In experiments to determine agonist activity, cells were exposed (4.5 min for hD2, 7.5 min for hD3) to increasing concentrations of putative agonist at half hour intervals. Seven concentrations of the putative agonist were used. Peak acidification rate to each putative agonist concentration was determined and concentration-response curves fitted using Robofit [Tilford, N.S., Bowen, W.P. & Baxter, G.S. Br. J. Pharmacol. (1995) in press]. In experiments to determine antagonist potency, cells were treated at 30 min intervals with five pulses of a submaximal concentration of quinpirole (100 nM for hD2 cells, 30 nM for hD3 cells), before exposure to the lowest concentration of putative antagonist. At the end of the next 30 min interval, cells were pulsed again with quinpirole (in the continued presence of the antagonist) before exposure to the next highest antagonist concentration. In all, five concentrations of antagonist were used in each experiment. Peak acidification rate to each agonist concentration was determined and concentration-inhibition curves fitted using Robofit.

Compounds of Examples tested according to this method were shown to be antagonists with pKb values within the range 7.0 - 10.0 at the human cloned dopamine D_3 receptor.

Pharmaceutical Formulations

The following represent typical pharmaceutical formulations according to the present invention, which may be prepared using standard methods.

IV Infusion

Compound of formula (I)	1-40 mg
Buffer	to pH ca 7
Solvent/complexing agent	to 100 ml

Bolus Injection

Compound of formula (I)	1-40 mg
Buffer	to pH ca 7
Co-Solvent	to 5 ml

Buffer : Suitable buffers include citrate, phosphate, sodium hydroxide/hydrochloric acid.

Solvent : Typically water but may also include cyclodextrins (1-100 mg) and co-solvents such as propylene glycol, polyethylene glycol and alcohol.

Tablet

Compound	1 - 40 mg
Diluent/Filler *	50 - 250 mg
Binder	5 - 25 mg
Disentegrant *	5 - 50 mg
Lubricant	1 - 5 mg
Cyclodextrin	1 - 100 mg

* may also include cyclodextrins

Diluent : e.g. Microcrystalline cellulose, lactose, starch

Binder : e.g. Polyvinylpyrrolidone, hydroxypropymethylcellulose

Disintegrant : e.g. Sodium starch glycollate, crospovidone

Lubricant : e.g. Magnesium stearate, sodium stearyl fumarate.

Oral Suspension

Compound	1 - 40 mg
Suspending Agent	0.1 - 10 mg
Diluent	20 - 60 mg
Preservative	0.01 - 1.0 mg
Buffer	to pH ca 5 - 8
Co-solvent	0 - 40 mg
Flavour	0.01 - 1.0 mg
Colourant	0.001 - 0.1 mg

Suspending agent : e.g. Xanthan gum, microcrystalline cellulose
Diluent : e.g. sorbitol solution, typically water
Preservative : e.g. sodium benzoate
Buffer : e.g. citrate
Co-solvent : e.g. alcohol, propylene glycol, polyethylene glycol, cyclodextrin

The invention is further illustrated by the following non-limiting examples :

Description 1

7-Bromo-1,2,3,4-tetrahydroisoquinoline

A mixture of 7-bromo-2-trifluoroacetyl-1,2,3,4-tetrahydoisoquinoline (G.E. Stokker, Tetrahedron Letters 1996, 37, 5453) (43.4g, 0.14 mol), potassium carbonate (104.3g, 0.75 mol), methanol (1L) and water (150ml) was heated at reflux for 1h, then cooled and evaporated *in vacuo*. Residue was partitioned between water (1L) and dichloromethane (4 x 200ml). Combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give an oil which was dissolved in hexane. The mixture was filtered and the filtrate evaporated *in vacuo* to give the title compound as an oil (17.7g, 60%).

^{1}H NMR ($CDCl_3$) δ: 1.77 (1H, br s), 2.73 (2H, t, J = 7 Hz), 3.13 (2H, t, J = 7 Hz), 3.98 (2H, s), 6.96 (1H, d, J = 9 Hz), 7.16 (1H, d, J = 2 Hz), 7.26 (1H, dd, J = 9, 2 Hz).

The following compounds were prepared in a similar manner to Description 1

(a) 7-Cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 159 (MH^+). $C_{10}H_{10}N_2$ requires 158.

(b) 5-Trifluoromethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 202 (MH^+). $C_{10}H_{10}F_3N$ requires 201.

(c) 5-Pentafluoroethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 252 (MH^+). $C_{11}H_{10}F_5N$ requires 251.

(d) 6-Pentafluoroethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 252 (MH$^+$). $C_{11}H_{10}F_3N$ requires 251

(e) 5,6-Difluoro-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 170 (MH$^+$). $C_9H_9F_2N$ requires 169.

Description 2

7-Cyano-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline

A mixture of 7-bromo-2- trifluoroacetyl -1,2,3,4-tetrahydroisoquinoline (51.7 g, 0.168 mol), copper (I) cyanide (31.8 g, 0.35 mol) and N-methyl-2-pyrrolidinone (620 ml) was heated at reflux for 4h, cooled, then partitioned between dilute aqueous ammonia (1.5 L) and dichloromethane (5 x 300ml). The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give the title compound (42.6 g, 100 %) as an oil.

Mass spectrum (API$^-$): Found 253 (M-H)$^-$. $C_{12}H_9F_3N_2O$ requires 254.

Description 3

2-(8-(1,4-Dioxa)spiro[4.5]decyl)acetaldehyde

A solution of 8-(2-hydroxyethyl)-1,4-dioxaspiro[4.5]decane (20.7g, 111 mmol) (M.A. Ciufolini, N.E. Byrne, J. Am. Chem. Soc. **113**, 8016 (1991)) in dimethylsulfoxide (800ml) was treated with triethylamine (150ml), followed by sulfur trioxide pyridine complex (56.2g, 350 mmol). The resulting mixture was stirred at room temperature for 0.5h, and saturated sodium bicarbonate (1L) was added with stirring. The resultant mixture was extracted with dichloromethane (3x1.5L) and the combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow oil which was purified by chromatography on silica gel (~300g) with 0-15% ethyl acetate in hexane gradient elution to give the title compound as a yellow oil (17.68g, 87%).

Mass spectrum (API$^+$): Found 185 (MH$^+$). $C_{10}H_{16}O_3$ requires 184.

^{1}H NMR ($CDCl_3$) δ: 1.34 (2H, m), 1.58 (2H, m), 1.75 (4H, m), 1.96 (1H, m), 2.37 (2H, dd, J = 7, 2 Hz), 3.94 (4H, s), 9.87 (1H, t, J = 2 Hz).

Description 4

8-(2-(2-(7-Cyano-1,2,3,4-tetrahydro)isoquinolyl)ethyl)-1,4-dioxaspiro[4.5]decane

A mixture of 2-(8-(1,4-dioxa)spiro[4.5]decyl)acetaldehyde (3.9g. 21.2 mmol), 7-cyano-1,2,3,4-tetrahdyroisoquinoline (3.35g, 21.2 mmol), sodium triacetoxyborohydride (6.8g, 32.1 mmol) and 1,2-dichloroethane (200ml) was stirred at room temperature for 16h. The reaction mixture was partitioned between dichloromethane (200ml), and saturated potassium carbonate (400ml). The organic extract was washed with brine (200ml), dried (Na_2SO_4) and evaporated *in vacuo* to give an oil, which was purified by filtration through silica gel (~100g) in ethyl acetate to give the title compound as an orange oil (6.11g, 88%).

Mass spectrum (API$^+$): Found 327 (MH^+). $C_{20}H_{26}N_2O_2$ requires 326.

^{1}H NMR ($CDCl_3$) δ: 1.35 (3H, m), 1.53 (4H, m), 1.72 (4H, m), 2.52 (2H, m), 2.73 (2H, t, J = 7 Hz), 2.94 (2H, m), 3.60 (2H, s), 3.93 (4H, s), 7.18 (1H, d, J = 9 Hz), 7.33 (1H, s), 7.41 (1H, d, J = 9 Hz).

Description 5

7-Cyano-2-(2-(1-(4-oxo)cyclohexyl)ethyl-1,2,3,4-tetrahydroisoquinoline

8-(2-(2-(7-cyano-1,2,3,4-tetrahydro)isoquinolyl)ethyl)-1,4-dioxaspiro[4.5]decane (5.9g, 18.1 mmol) was dissolved in a mixture of tetrahydrofuran (600ml), and water (600ml), then concentrated sulfuric acid (2.65g, 27 mmol) was added and the mixture was stirred at room temperature for 66h. The reaction mixture was evaporated *in vacuo* and the residues partitioned between ethyl acetate (1L) and saturated potassium carbonate (400ml). The organic extract was dried (Na_2SO_4) and evaporated *in vacuo* to give the title compound as a brown oil (5.1g, 100%).

Mass spectrum (API$^+$): Found 283 (MH^+). $C_{18}H_{22}N_2O$ requires 282.

^{1}H NMR ($CDCl_3$) δ: 1.44 (2H, m), 1.62 (2H, m), 1.85 (1H, m), 2.11 (3H, m), 2.38 (3H, m), 2.61 (2H, m), 2.78 (2H, m), 2.96 (2H, m), 3.64 (2H, s), 7.21 (1H, d, J = 9 Hz), 7.34 (1H, s), 7.43 (1H, d, J = 9 Hz).

Description 6

***cis* and *trans*-2-(2-(1-(4-Amino)cyclohexyl)ethyl-7-cyano-1,2,3,4-tetrahydroisoquinoline**

A mixture of 7-cyano-2-(2-(1-(4-oxo)cyclohexyl)ethyl-1,2,3,4-tetrahydroisoquinoline (4.5g, 15.9 mmol), ammonium acetate (12.5g, 158 mmol) sodium cyanoborohydride (6.9g, 110 mmol) and methanol (225ml) was heated at reflux for 1h, then cooled and acidified to pH2 with 5N hydrochloric acid. The mixture was then basified using 2M sodium hydroxide and extracted with dichloromethane (2x400ml). Combined extracts

were dried (Na_2SO_4) and evaporated *in vacuo* to give the title compound as a brown oil (4.12g, 92%).

Mass spectrum (API$^+$): Found 284 (MH^+). $C_{18}H_{25}N_3$ requires 283

^1H NMR ($CDCl_3$) δ: 0.92 - 1.19 (3H, m), 1.26 (1H, m), 1.46 - 1.65 (5H, m), 1.72 - 2.03 (5H, m), 2.53 (2H, m), 2.72 (2H, m), 2.94 (2H, t, J = 7 Hz), 3.60 (2H, s), 7.18 (1H, d, J = 8 Hz), 7.32 (1H, s), 7.41 (1H, d, J = 8 Hz).

Description 7

6-Cyano-1,2,3,4-tetrahydroisoquinoline

Prepared in a similar manner to that described in H.G. Selnick *et al.*, Synthetic Communications **25** (20) 3255 (1995).

Mass spectrum (API$^+$): Found 159 (MH^+). $C_{10}H_{10}N_2$ requires 158.

^1H NMR ($CDCl_3$) δ: 2.47 (1H, br s), 2.82 (2H, m), 3.15 (2H, m), 4.05 (2H, s), 7.10 (1H, d, J = 8 Hz), 7.40 (2H, m).

The following compound was prepared in a similar manner to Description 7

(a) 2-*t*-Butyloxycarbonyl-8-cyano-1,2,3,4-tetrahydroisoquinoline

^1H NMR ($CDCl_3$) δ: 1.51 (9H, s), 2.87 (2H, m), 3.68 (2H, m), 4.76 (2H, s), 7.26 (1H, m), 7.37 (1H, d, J = 7 Hz), 7.52 (1H, d, J = 7 Hz).

Description 8

***trans*-2-(1-(4-(*N*- *tert*-Butyloxycarbonyl)amino)cyclohexyl)acetic acid, methyl ester**

A mixture of *trans*-(4-amino)cyclohexylactic acid hydrogen sulfate (T.P. Johnston *et al*; J. Med Chem., 1977, 20 (2), 279-290), (27.0g, 106mmol), conc. H_2SO_4 (3ml), and methanol (300ml) was stirred at reflux for 5h. Resulting solution was filtered and the filtrate evaporated *in vacuo* to give a brown oil (36g). A mixture of this material, triethylamine (36ml; 26.1g, 259 mmol), dichloromethane (600ml) and di-*t*-butyl dicarbonate (25.5g, 117mmol) was stirred at 20°C for 18h. Resulting solution was partitioned between saturated aqueous $NaHCO_3$ (500ml) and dichloromethane (3x200ml), and the combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give the title compound (24.6g, 86%) as a colourless solid.

^{1}H NMR ($CDCl_3$) δ: 1.08 (4H, m), 1.43 (9H, s), 1.76 (3H, m), 2.00 (2H, m), 2.20 (2H, d, J = 7 Hz), 3.37 (1H, m), 3.66 (3H, s), 4.39 (1H, br s).

Description 9

***trans*-2-(1-(4-(*N-tert*-Butyloxycarbonyl)amino)cyclohexyl)acetaldehyde**

To a stirred solution of *trans*-2-(1-(4-(*N-tert*-butyloxycarbonyl)amino)cyclohexyl)acetic acid, methyl ester (46.0g, 170 mmol) in dry toluene (920ml) at -78°C under argon was added a solution of di-isobutylaluminium hydride (1M; 285 ml; 285 mmol), dropwise over 0.5h. Resulting solution was stirred for a further 0.3h and quenched with a mixture of methanol (28ml) in toluene (50ml) and then poured into saturated aqueous potassium sodium tartrate (1.2L). The resultant mixture was extracted with ether (4x1L). The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give a waxy solid which was purified using silica gel, eluting with 10-50% ethyl acetate/hexane to give the title compound (21.77g, 53%) as a colourless solid.

^{1}H NMR ($CDCl_3$) δ: 1.12 (4H, m), 1.44 (9H, s), 1.78 (3H, m), 2.00 (2H, m), 2.33 (2H, dd, J = 7, 2 Hz), 3.37 (1H, m), 4.40 (1H, m), 9.75 (1H, m).

Description 10

***trans*-2-(2-(1-(4-(*N-tert*-Butyloxycarbonyl)amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline**

A mixture of *trans*-2-(1-(4-(*N-tert*-butyloxycarbonyl)amino)cyclohexyl)acetaldehyde (6.0g, 24.9 mmol), 6-cyano-1,2,3,4-tetrahydroisoquinoline (3.93g, 24.9 mmol), sodium triacetoxyborohydride (7.7g, 36.3 mmol) in 1,2-dichloroethane (270ml) was stirred at 20°C for 16h. Resulting solution was partitioned between aqueous K_2CO_3 (200ml) and dichloromethane (100ml), and the combined extracts were washed with brine (200ml), dried (Na_2SO_4) and evaporated *in vacuo* to a minimum volume and filtered through a pad of silica (100g), washing with ethyl acetate. The filtrate was evaporated *in vacuo* to give the title compound (8.33g, 87%) as a yellow solid.

^{1}H NMR ($CDCl_3$) δ: 1.08 (4H, m), 1.28 (1H, m), 1.44 (9H, s), 1.48 (2H, m), 1.78 (2H, m), 1.99 (2H, m), 2.52 (2H, m), 2.72 (2H, t, J = 7 Hz), 2.91 (2H, ,m), 3.37 (1H, m), 3.63 (2H, m), 4.40 (1H, m), 7.12 (1H, d, J = 8 Hz), 7.39 (2H, m).

The following compounds were prepared in a similar manner to Description 10.

(a) *trans*-2-(2-(1-(4-(*N- tert*-Butyloxycarbonyl)amino)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline

^{1}H NMR ($CDCl_3$) δ: 1.06 (4H, m), 1.28 (1H, m), 1.44 (9H, s), 1.47 (2H, m), 1.77 (2H, m), 1.99 (2H, m), 2.52 (2H, m), 2.72 (2H, t, J = 7 Hz), 2.94 (2H, m), 3.37 (1H, m), 3.60 (2H, s), 4.37 (1H, m), 7.18 (1H, d, J = 8 Hz), 7.32 (1H, s), 7.39 (1H, d, J = 8 Hz).

(b) *trans*-2-(2-(1-(4-(*N*- *tert*-Butyloxycarbonyl)amino)cyclohexyl)ethyl)-5-cyano-1,2,3,4-tetrahydroisoquinoline

^{1}H NMR ($CDCl_3$) δ: 1.07 (4H, m), 1.28 (1H, m), 1.45 (9H, s), 1.49 (2H, m), 1.71 (2H, m), 2.01 (2H, m), 2.55 (2H, m), 2.78 (2H, t, J = 7 Hz), 3.07 (2H, t, J = 7 Hz), 3.38 (1H, m), 3.62 (2H, s), 4.39 (1H, m), 7.23 (2H, m), 7.49 (1H, dd, J = 9, 2 Hz).

(c) *trans*-2-(2-(1-(4-*N*- *tert*-Butyloxycarbonyl)methylamino)cyclohexyl)ethyl-7-cyano-1,2,3,4-tetrahydroisoquinoline

^{1}H NMR ($CDCl_3$) δ: 1.10 (2H, m), 1.25 (1H, m), 1.40 (2H, m), 1.46 (9H, s), 1.50 (2H, m), 1.68 (2H, m), 1.84 (2H, m), 2.54 (2H, m), 2.73 (5H, m), 2.95 (2H, m), 3.59 (2H, s), 3.90 (1H, m), 7.18 (1H, d, J = 9 Hz), 7.31 (1H, d, J = 1Hz), 7.40 (1H, dd, J = 9, 1 Hz).

(d) *trans*-6-Bromo-2-(2-(1-(4-*N*- *tert*-Butyloxycarbonyl)amino)cyclohexyl)ethyl-1,2,3,4-tetrahydroisoquinoline

Mass Spectrum (API$^+$): Found 437 (MH^+). $C_{22}H_{33}{}^{79}BrN_2O_2$ requires 436.

(e) *trans*-2-(2-(1-(4-*N*- *tert*-Butyloxycarbonyl)amino)cyclohexyl)ethyl-6-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline

Mass Spectrum (API$^+$): Found 427 (MH^+). $C_{23}H_{33}F_3N_2O_2$ requires 426.

(f) *trans*-2-(2-(1-(4-*N*- *tert*-butyloxycarbonyl)amino)cyclohexyl)ethyl-6-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline

Mass Spectrum (API$^+$): Found 443 (MH^+). $C_{23}H_{33}F_3N_2O_3$ requires 442.

(g) *trans*-2-(2-(1-(4-(*N*-*t*-Butyloxycarbonyl)amino)cyclohexyl)ethyl)-7-cyano-5-methyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 398 (MH^+). $C_{24}H_{35}N_3O_2$ requires 397.

(h) *trans*-2-(2-(1-(4-(*N*-*t*-Butyloxycarbonyl)amino)cyclohexyl)ethyl)-7-cyano-6-methyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 398 (MH^+). $C_{24}H_{35}N_3O_2$ requires 397.

(i) *trans*-2-(2-(1-(4-(*N*-*t*-Butyloxycarbonyl)amino)cyclohexyl)ethyl)-6-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 427 (MH$^+$). $C_{23}H_{33}F_3N_2O_2$ requires 426.

(j) *trans*-2-(2-(1-(4-(*N*-*t*-Butyloxycarbonyl)amino)cyclohexyl)ethyl)-6-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 443 (MH$^+$). $C_{23}H_{33}F_3N_2O_3$ requires 442.

(k) *trans*-2-(2-(1-(4-(*N*-*t*-Butyloxycarbonyl)amino)cyclohexyl)ethyl)-5-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 427 (MH$^+$). $C_{23}H_{33}F_3N_2O_2$ requires 426.

(l) *trans*-2-(2-(1-(4-(*N*-*t*-Butyloxycarbonyl)amino)cyclohexyl)ethyl)-5-pentafluoroethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 477 (MH$^+$). $C_{24}H_{33}F_5N_2O_2$ requires 476.

(m) *trans*-2-(2-(1-(4-(*N*-*t*-Butyloxycarbonyl)amino)cyclohexyl)ethyl)-6-pentafluoroethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 477 (MH$^+$). $C_{24}H_{33}F_5N_2O_2$ requires 476.

(n) *trans*-2-(2-(1-(4-(*N*-*t*-Butyloxycarbonyl)amino)cyclohexyl)ethyl)-8-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 384 (MH$^+$). $C_{23}H_{33}N_3O_2$ requires 383.

^{1}H NMR ($CDCl_3$) δ: 1.00 - 1.60 (16H, m), 1.69 - 2.10 (4H, m), 2.54 - 2.61 (2H, m), 2.72 (2H, m), 2.92 (2H, m), 3.37 (1H, br s), 3.77 (2H, s), 4.38 (1H, br s), 7.21 (1H, t, J = 7 Hz), 7.33 (1H, d, J = 7 Hz), 7.45 (1H, d, J = 7 Hz).

(o) *trans*-2-(2-(1-(4-(*N*-*t*-Butyloxycarbonyl)amino)cyclohexyl)ethyl-5,6-difluoro-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 395 (MH$^+$). $C_{22}H_{32}F_2N_2O_2$ requires 394.

Description 11

***trans*-2-(2-(1-(4-Amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline**

A mixture of *trans*-2-(2-(1-(4-(*N- tert*-butyloxycarbonyl)amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline (8.3g, 21.7 mmol), trifluoroacetic acid (15ml) and dichloromethane (180ml) was stirred at 20°C for 2h. Resulting solution was evaporated *in vacuo* and the residue partitioned between saturated aqueous K_2CO_3 (200ml) and dichloromethane (2x100ml). The combined organic extracts were washed with brine (100ml), dried (Na_2SO_4) and evaporated *in vacuo* to give the title compound (4.99g, 81%) as a brown oil.

Mass spectrum (API$^+$): Found 284 (MH^+). $C_{18}H_{25}N_3$ requires 283.

^{1}H NMR ($CDCl_3$) δ: 0.91 - 1.16 (4H, m), 1.22 - 1.40 (3H, m), 1.47 (2H, m), 1.72 - 1.91 (4H, m), 2.52 (2H, m), 2.59 (1H, m), 2.72 (2H, t, J = 7 Hz), 2.92 (2H, m), 3.64 (2H, s), 7.11 (1H, d, J = 8 Hz), 7.39 (2H, m).

The following compounds were prepared in a similar manner to Description 11

(a) *trans*-2-(2-(1-(4-Amino)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 284 (MH^+). $C_{18}H_{25}N_3$ requires 283.

^{1}H NMR ($CDCl_3$) δ: 0.91 - 1.16 (4H, m), 1.18 - 1.40 (3H, m), 1.47 (2H, m), 1.73 - 1.92 (4H, m), 2.53 (2H, m), 2.62 (1H, m), 2.72 (2H, t, J = 7 Hz), 2.94 (2H, m), 3.60 (2H, s), 7.19 (1H, d, J = 8 Hz), 7.32 (1H, s), 7.41 (1H, d, J = 8 Hz).

(b) *trans*-2-(2-(1-(4-Amino)cyclohexyl)ethyl)-5-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 284 (MH^+). $C_{18}H_{25}N_3$ requires 283.

^{1}H NMR ($CDCl_3$) δ: 0.92 - 1.18 (4H, m), 1.28 (1H, m), 1.50 (4H, m), 1.84 (4H, m), 2.48 - 2.70 (3H, m), 2.79 (2H, t, J = 7 Hz), 3.06 (2H, t, J = 7 Hz), 3.64 (2H, m), 7.24 (2H, m), 7.49 (1H, dd, J = 9, 2 Hz).

(c) *trans*-7-Cyano-2-(2-(1-(4-methylamino)cyclohexyl)ethyl)1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 298 (MH^+). $C_{19}H_{27}N_3$ requires 297.

(d) *trans*-2-(2-(1-(4-Amino)cyclohexyl)ethyl)-6-bromo-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 337 (MH^+). $C_{17}H_{25}{}^{79}BrN_2$ requires 336.

(e) *trans*-2-(2-(1-(4-Amino)cyclohexyl)ethyl)-6-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 327 (MH$^+$). $C_{18}H_{25}F_3N_2$ requires 326.

(f) *trans*-2-(2-(1-(4-Amino)cyclohexyl)ethyl)-6-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 343 (MH$^+$). $C_{18}H_{25}F_3N_2O$ requires 342.

(g) *trans*-2-(2-(1-(4-Amino)cyclohexyl)ethyl)-7-cyano-5-methyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 298 (MH$^+$). $C_{19}H_{27}N_3$ requires 297.

(h) *trans*-2-(2-(1-(4-Amino)cyclohexyl)ethyl)-7-cyano-6-methyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 298 (MH$^+$). $C_{19}H_{27}N_3$ requires 297.

(i) *trans*-2-(2-(1-(4-Amino)cyclohexyl)ethyl)-6-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 327 (MH$^+$). $C_{18}H_{25}F_3N_2$ requires 326.

(j) *trans*-2-(2-(1-(4-Amino)cyclohexyl)ethyl)-6-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 343 (MH$^+$). $C_{18}H_{25}F_3N_2O$ requires 342.

(k) *trans*-2-(2-(1-(4-Amino)cyclohexyl)ethyl)-5-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 327 (MH$^+$). $C_{18}H_{25}F_3N_2$ requires 326.

(l) *trans*-2-(2-(1-(4-Amino)cyclohexyl)ethyl)-5-pentafluoroethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 377 (MH$^+$). $C_{19}H_{25}F_5N_2$ requires 376.

(m) *trans*-2-(2-(1-(4-Amino)cyclohexyl)ethyl)-6-pentafluoroethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 377 (MH$^+$). $C_{19}H_{25}F_5N_2$ requires 376.

(n) *trans*-2-(2-(1-(4-Amino)cyclohexyl)ethyl)-8-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 284 (MH$^+$). $C_{18}H_{25}N_3$ requires 283.

^{1}H NMR ($CDCl_3$) δ: 0.98 - 1.29 (9H, m), 1.70 - 1.90 (4H, m), 2.50 - 2.65 (3H, m), 2.73 (2H, m), 2.92 (2H, m), 3.78 (2H, s), 7.21 (1H, t, J = 7 Hz), 7.33 (1H, d, J = 7 Hz), 7.45 (1H, d, J = 7 Hz).

(o) *trans*-2-(2-(1-(4-Amino)cyclohexyl)ethyl)-5,6-difluoro-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 295 (MH$^+$). $C_{17}H_{24}F_2N_2$ requires 294.

Description 12

(*E*)-3-(3-Methylsulfonyl)phenylpropenoic acid

A mixture of methyl phenyl sulfone (15.0g, 96 mmol), water (180ml) and sulfuric acid (98%; 180ml) was treated with *N*-bromosuccinimide (17.2g, 96.6 mmol) then stirred at 85 - 90°C for 4h. Mixture was cooled, then partitioned between water (200ml) and ether (3 x 150ml). Combined organic extracts were washed with 10% aqueous NaOH (200ml), dried (Na_2SO_4) and evaporated *in vacuo* to give a solid (19.4g). The latter was heated at 140°C with triethylamine (22ml; 0.155 mol), ethyl acrylate (16.8ml; 0.155 mol), tri-(2-tolyl)phosphine (3.0g, 10 mmol) and palladium (II) acetate (1.1g, 5 mmol) in acetonitrile (20ml) under argon with stirring for 2h. Mixture was cooled, then partitioned between ether (500ml) and water (3 x 300ml). Organic phase was dried (Na_2SO_4) and evaporated *in vacuo* to give a solid. Chromatography on silica eluting with 20 - 100% ethyl acetate - hexane gave a solid (20.2g), which was heated with sodium hydroxide (6.4g, 0.16 mol) and water (500ml) at reflux for 3h. Resultant was cooled, then washed with ethyl acetate (500ml). Aqueous phase was acidified with 10M HCl (16ml) and resulting solid filtered, to give the title compound (15.5g, 71%) as a colourless solid.

Mass spectrum (API$^-$): Found 225 (M-H$^-$). $C_{10}H_{10}O_4S$ requires 226.

^{1}H NMR (DMSO-d_6) δ: 3.40 (3H, s), 6.845 (1H, d, J = 16 Hz), 7.79 (1H, t, J = 8 Hz), 7.80 (1H, d, J = 16 Hz), 8.05 (1H, d, J = 8 Hz), 8.18 (1H, d, J = 8 Hz), 8.36 (1H, s), 12.75 (1H, br s).

Description 13

6-Cyanoindole-2-carboxylic acid

A solution of 4-cyanobenzaldehyde (1.27g, 9.69 mmol) and ethyl azidoacetate (5g, 38.76 mmol) in methanol (6ml) was added dropwise over 0.16h to a stirred solution of sodium methoxide (2.143g, 39.7 mmol) in methanol (24ml) at -8°C. The reaction was stirred

with ice cooling for a further 3h before being poured into ice/water (500ml). The precipitate was filtered, washed with water and dried *in vacuo*. A sample of the residue (0.55g) was dissolved in xylene (15ml) and added dropwise to refluxing xylene (35ml) over 0.75h. After a further 1.5h reflux the mixture was cooled and the precipitate filtered, washed with a small amount of xylene and dried *in vacuo*. The residue was dissolved in aqueous methanol (20ml, 1:1) and sodium hydroxide (1 equivalent) added. The mixture was stirred at room temperature for 18h, concentrated to half volume and poured into water (50ml). The resultant solution was washed with ethyl acetate (50ml) and the aqueous layer acidified with 2N HCl. The precipitate was filtered, washed with water and dried *in vacuo* to afford the title compound as a pale yellow solid (0.209g, 11%).

^{1}H NMR (DMSO-d_6) δ: 7.25 (1H, d, J = 1 Hz), 7.46 (1H, dd, J = 8, 1 Hz), 7.91 (2H, m), 12.40 (1H, s), 13.40 (1H, br s).

Description 14

5-Bromo-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline

Prepared using a method similar to that described in G.E. Stokker, Tetrahedron Letters 1996, **37**, 5453, in 90% yield.

^{1}H NMR ($CDCl_3$) δ: 2.97 (2H, m), 3.90 (2H, m), 4.75 and 4.82 (2H, 2 x s), 7.13 (2H, m), 7.52 (1H, m).

The following compounds were prepared in a similar manner to Description 14

(a) 7-Bromo-5-methyl-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline

^{1}H NMR ($CDCl_3$) δ: 2.25 (3H, s), 2.77 (2H, m), 3.88 (2H, m), 4.70 and 4.76 (2H, 2 x s), 7.15 and 7.24 (1H, 2 x m), 7.24 and 7.43 (1H, 2 x m).

(b) 2-Trifluoroacetyl-5-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 298 (MH^+). $C_{12}H_9F_6NO$ requires 297.

(c) 5,6-Difluoro-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 266 (MH^+). $C_{11}H_8F_5NO$ requires 265.

Description 15

5-Cyano-1,2,3,4-tetrahydroisoquinoline

Treatment of 5-bromo-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline in a manner similar to Description 2 gave the title compound (3.95g, 86%) as a solid.

Mass spectrum (API$^+$): Found 159 (MH^+). $C_{10}H_{10}N_2$ requires 158.

^{1}H NMR (DMSO-d_6) δ: 3.15 (2H, m), 3.51 (2H, m), 4.30 (2H, m), 7.45 (1H, t, J = 9 Hz), 7.68 (1H, d, J = 9 Hz), 7.80 (1H, d, J = 9 Hz), 9.87 (2H, br s), (.HCl salt).

The following compound was prepared in a similar manner to Description 15

(a) 7-Cyano-5-methyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 173 (MH^+). $C_{11}H_{12}N_2$ requires 172.

Description 16

2-(1-(4-(*N*- *tert*-Butyloxycarbonyl)methylamino)cyclohexyl)ethanol

A mixture of 2-(1-(4-(*N*- *tert*-butyloxycarbonyl)amino)cyclohexyl)acetic acid, methyl ester (2.10g, 7.75 mmol), lithium aluminium hydride (0.62g, 16.3 mmol) and ether (100ml) was heated at reflux for 1.5h, cooled, then treated dropwise with ice cooling, with saturated aqueous potassium sodium tartrate. Resulting supernatant solution was decanted off and evaporated *in vacuo* to give an oil (1.3g). Chromatography on silica eluting with 50% ethyl acetate-hexane gave 2-(1-(4-(*N*- *tert*-butyloxycarbonyl)amino)cyclohexyl)ethanol. Further evaluation with 90:10:1 ethyl acetate-methanol- .880 ammonia gave a solid (0.64g) which was treated wtih di-*t*-butyl dicarbonate (0.99g, 4.5 mmol) in dichloromethane (20ml) at 20°C for 3h. Mixture was evaporated *in vacuo* to give an oil. Chromatography on silica with 25-100% ethyl acetate - hexane gradient elution gave the title compound (0.89g, 45%) as an oil.

^{1}H NMR ($CDCl_3$) δ: 1.11 (2H, m), 1.25 - 1.54 (6H, m), 1.47 (9H, s), 1.68 (2H, m), 1.84 (2H, m), 2.72 (3H, s), 3.69 (2H, t, J = 6 Hz), 3.95 (1H, br s).

Description 17

2-(1-(4-(*N*- *tert*-Butyloxycarbonyl)methylamino)cyclohexyl)acetaldehyde

To a stirred solution of oxalyl chloride (0.33ml; 3.9 mmol) in dichloromethane (20ml) under argon at -65°C was added dry dimethyl sulfoxide (0.58ml; 82 mmol). Mixture was stirred at -65°C for 0.2 h then a solution of 2-(1-(4-(*N*- *tert*-butyloxycarbonyl)methylamino)cyclohexyl)ethanol (0.87g, 3.4 mmol) in dichloromethane (5ml) was added dropwise over 0.1h. Mixture was stirred at -70°C for 1h, then triethylamine (2.5ml; excess) was added dropwise and resultant stirred at -70°C for 2h then at 20°C for 18h. Resulting mixture was evaporated *in vacuo* and residue

partitioned between ether (80ml) and water (80ml). Organic phase was washed with water (3 x 50 ml), dried (Na_2SO_4) and evaporated *in vacuo* to give the title compound (0.80g, 93%) as an oil.

^{1}H NMR ($CDCl_3$) δ: 1.14 (2H, m), 1.43 (1H, m), 1.45 (9H, s), 1.50 (2H, m), 1.68 (2H, m), 1.83 (2H, m), 2.34 (2H, dd, J = 7, 2 Hz), 2.72 (3H, s), 3.95 (1H, m), 9.77 (1H, t, J = 2 Hz).

Description 18

(*E*)-3-(3-Acetyl)phenylpropenoic acid

A mixture of 3-bromoacetophenone (1.99 g, 10 mmol), acrylic acid (0.8 g, 11 mmol), palladium (II) acetate (1.1 mg, 0.005 mmol), triphenylphosphine (0.026 g, 0.1 mmol) and tri-n-butylamine (5 ml, 21 mmol) were heated at 150°C under argon for 2.5 h. After cooling, water (20 ml) was added, followed by $NaHCO_3$ (2 g). The aqueous layer was separated, washed with dichloromethane and acidified with 5N Hcl. The precipitate was filtered, washed with water and dried to afford the title compound as a pale yellow solid (0.64 g, 34%).

Mass spectrum (API$^-$): Found 189 (M-H$^-$). $C_{11}H_{10}O_2$ requires 190.

^{1}H NMR (DMSO-d_6) δ: 2.68 (3H, s), 6.73 (1H, d, J = 16 Hz), 7.62 (1H, m), 7.73 (1H, d, J = 16 Hz), 8.01 (2H, m), 8.30 (1H, s), 12.55 (1H, br s).

Description 19

(*E*)-3-(Acetamido)phenylpropenoic acid

Prepared from 3-bromoacetanilide in a similar manner to that of Description 18, to afford the title compound as a colourless solid (1.29 g, 63%).

Mass spectrum (API$^-$): Found 204 (M-H$^-$). $C_{11}H_{11}NO_3$ requires 205.

^{1}H NMR (DMSO-d_6) δ: 2.21 (3H, s), 6.56 (1H, d, J = 16 Hz), 7.50 (2H, m), 7.67 (1H, d, J = 16 Hz), 7.73 (1H, m), 7.99 (1H, s), 10.20 (1H, s), 12.60 (1H, br s).

Description 20

(3-Trifluoromethoxy)phenylethylamine hydrochloride

To a stirred solution of zirconium (IV) chloride (11.8g, 49.5 mmol) in dry tetrahydrofuran (200ml) at 20°C under argon was added, portionwise, sodium

borohydride (7.5g, 0.197 mol). Mixture was stirred for 1h, then 3-trifluoromethoxyphenylacetonitrile (4.2g, 20.9 mmol) was added. Stirring was continued for 24h, then water (110 ml) was added dropwise, keeping the internal temperature below 10°C. The mixture was partitioned between dilute aqueous ammonia (500ml) and ethyl acetate (4x100ml). Organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give an oil which was treated with ethereal HCl to give the title compound (2.1g, 50%).

Mass spectrum (API^+): Found 206 (MH^+). $C_9H_{10}F_3NO$ requires 205.

The following compounds were prepared in a similar manner to description 20.

(a) (3-Trifluoromethyl)phenethylamine hydrochloride

Mass spectrum (API^+): Found 190 (MH^+). $C_9H_{10}F_3N$ requires 189.

(b) (3-Bromo)phenethylamine hydrochloride

Mass spectrum (API^+): Found 200 (MH^+). $C_8H_{10}{}^{79}BrN$ requires 199.

(c) (4-Bromo-2-methyl)phenethylamine hydrochloride

NMR (DMSO-d_6) δ: 2.27 (3H, s), 2.88 (4H, m), 7.14 (1H, d, J = 8 Hz), 7.34 (1H, dd, J = 8, 2 Hz), 7.40 (1H, d, J = 2 Hz), 8.20 (3H, br s).

(d) (4-Bromo-3-methyl)phenethylamine hydrochloride

Mass spectrum (API^+): Found 216 (MH^+). $C_9H_{12}{}^{81}BrN$ requires 215.

(e) (2-Trifluoromethyl)phenethylamine hydrochloride

Mass spectrum (API^+): Found 190 (MH^+). $C_9H_{10}F_3N$ requires 189.

(f) (2,3-Difluoro)phenethylamine hydrochloride

Mass spectrum (API^+): Found 158 (MH^+). $C_8H_9F_2N$ requires 157.

Description 21

***N*-(2-(3-Trifluoromethoxyphenyl)ethyl)trifluoroacetamide**

To a stirred mixture of (3-trifluoromethoxy)phenethylamine hydrochloride (5.85g, 24.2 mmol) and 2,6-lutidine (5.65ml; 5.19g, 48.6 mmol) in dichloromethane (100ml) at 0°C under argon was added, dropwise, trifluoroacetic anhydride (3.42ml, 5.08g, 24.2 mmol). Resultant was stirred at 20°C for 18h then partitioned between water (100ml) and dichloromethane (2x100ml). Organic phase was washed with 1M hydrochloric acid (100ml), saturated aqueous $NaHCO_3$ (100ml), dried (Na_2SO_4) then evaporated *in vacuo* to give the title compound (6.14g, 84%) as an oil.

Mass spectrum (API^+): Found 302 (MH^+). $C_{11}H_9F_6NO_2$ requires 301.

The following compounds were prepared in a similar manner to description 21.

(a) *N*-(2-(3-Trifluoromethylphenyl)ethyl)trifluoroacetamide

Mass spectrum (API^-): Found 284 $(M-H)^-$. $C_{11}H_9F_6NO$ requires 285.

(b) *N*-(2-(3-Bromophenyl)ethyl)trifluoroacetamide

Mass spectrum (API^-): Found 294 $(M-H)^-$. $C_{10}H_9{}^{79}BrF_3NO$ requires 295.

(c) *N*-(2-(4-Bromo-2-methylphenyl)ethyl)trifluoroacetamide

^1H NMR ($CDCl_3$) δ: 2.33 (3H, s), 2.85 (2H, t, J = 7 Hz), 3.55 (2H, q, J = 7 Hz), 6.45 (1H, br s), 6.94 (1H, d, J = 8 Hz), 7.29 (1H, dd, J = 8, 2 Hz), 7.35 (1H, d, J = 2 Hz).

(d) *N*-(2-(4-Bromo-3-methylphenyl)ethyl)trifluoroacetamide

^1H NMR ($CDCl_3$) δ: 2.41 (3H, s), 2.83 (2H, t, J = 7 Hz), 3.60 (2H, q, J = 7 Hz), 6.30 (1H, br s), 6.89 (1H, dd, J = 8, 2 Hz), 7.09 (1H, d, J = 2 Hz), 7.49 (1H, d, J = 8 Hz).

(e) *N*-(2-(2-Trifluoromethylphenyl)ethyl)trifluoroacetamide

Mass spectrum (API^+): Found 284 $(M-H)^+$. $C_{11}H_9F_6NO$ requires 285.

(f) *N*-(2-(2,3-Difluorophenyl)ethyl)trifluoroacetamide

Mass spectrum (API^+): Found 252 $(M-H)^+$. $C_{10}H_8F_5NO$ requires 253.

Description 22

6-Trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride

N-(2-(3-Trifluoromethoxyphenyl)ethyl)trifluoroacetamide (6.14g, 19.6mmol) was treated in a manner similar to that described in G.E. Stokker, Tetrahedron Letters 37 5453 1996. The resulting product (6.13g) was treated with anhydrous potassium carbonate (15.0g, 0.108mol) in methanol (140ml) containing water (22ml) at reflux for 2 h. The mixture was cooled, evaporated *in vacuo*, then partitioned between water (200ml) and dichloromethane (4x50ml). Combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give an oil (4.14g), which was treated with ethereal HCl. Recrystallisation of the resulting solid from ethanol gave the title compound (2.33g, 45%) as a colourless solid.

^{1}H NMR (DMSO-d_6) δ: 3.07 (2H, t, J = 7 Hz), 3.39 (2H, t, J = 7 Hz), 4.29 (2H, s), 7.27 (1H, d, J = 9 Hz), 7.32 (1H, s), 7.40 (1H, d, J = 9 Hz), 9.81 (2H, br s).

Mass spectrum (API$^+$): Found 218 (MH^+). $C_{10}H_{10}F_3NO$ requires 217.

The following compounds were prepared in a similar manner to description 22.

(a) 6-Trifluoromethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride

Mass spectrum (API$^+$): Found 202 (MH^+). $C_{10}H_{10}F_3N$ requires 201.

(b) 6-Bromo-1,2,3,4-tetrahydroisoquinoline hydrochloride

^{1}H NMR (DMSO-d_6) δ: 3.08 (2H, t, J = 7Hz), 3.35 (2H, t, J = 7Hz), 4.23 (2H, s), 7.15 (1H, d, J = 9 Hz), 7.36 (1H, d, J = 9 Hz), 7.39 (1H, s).

(c) 7-Bromo-6-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride

^{1}H NMR (DMSO-d_6) δ: 2.32 (3H, s), 2.94 (2H, t, J = 6 Hz), 3.33 (2H, t, J = 6 Hz), 4.20 (2H, s), 7.21 (1H, s), 7.50 (1H, s), 9.64 (2H, br s).

Description 23

6-Cyano-1,2,3,4-tetrahydroisoquinoline hydrochloride

As an alternative procedure to that contained within Description 7, a solution of 6-bromo-1,2,3,4-tetrahydroisoquinoline hydrochloride (6.0g, 24 mmol) and triethylamine (7.4ml, 5.36g, 53 mmol) in dichloromethane (100ml) was treated with trifluoroacetic anhydride (3.7ml, 5.54g, 26.4 mmol) with ice cooling. Mixture was stirred at 20°C for

1.5h. then partitioned between saturated aqueous $NaHCO_3$ (250ml) and dichloromethane (3x50ml). Combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give a solid (8.3g). A mixture of the latter with copper (I) cyanide (5.1g, 56.6 mmol) in 1-methyl-2-pyrrolidinone (100ml) was heated at reflux under argon for 4h, then cooled and partitioned between water (300ml), .880 aqueous ammonia (100ml) and dichloromethane (5x200ml). Combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give an oil. The latter was dissolved in ether and treated with ethereal HCl to give the title compound (4.47g, 85%) as a colourless solid.

Mass spectrum (API^+): Found 159 (MH^+). $C_{10}H_{10}N_2$ requires 158.

The following compound was prepared in a similar manner to description 23

(a) 7-Cyano-6-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride

Mass spectrum (API^+): Found 173 (MH^+). $C_{11}H_{12}N_2$ requires 172.

Description 24

8-Cyano-1,2,3,4-tetrahydroisoquinoline

A mixture of 2-*t*-butyloxycarbonyl-8-cyano-1,2,3,4-tetrahydroisoquinoline (1.4g, 5.4 mmol) and trifluoroacetic acid (2ml) in dichloromethane (20ml) was stirred at 40°C for 16h. Mixture was evaporated *in vacuo* and the resulting residue partitioned between dichloromethane and saturated potassium carbonate solution. The aqueous layer was extracted with more dichloromethane (2x100ml). The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to afford the desired product as an amber oil (0.9g, 100%).

Mass spectrum (API^+): Found 159 (MH^+). $C_{10}H_{10}N_2$ requires 158.

Description 25

2-*t*-Butoxycarbonyl-8-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinoline

A solution of 8-hydroxy-1,2,3,4-tetrahydroisoquinoline (2.55g, 17 mmol) and di-*tert*-butyl dicarbonate (3.9g, 17.9 mmol) in THF (250ml) was allowed to stir at room temperature. The THF was removed *in vacuo* and the resulting residue purified by flash silica gel chromatography, eluted with dichloromethane to give an oil. An aliquot of this (3.2g, 13 mmol) was dissolved in dry dichloromethane (50ml). To this solution at -20°C under argon, was added triethylamine (2.1ml), followed by trifluoromethylsulfonic anhydride (2.4ml, 14 mmol) in dichloromethane (2ml) dropwise. The mixture was stirred from -20°C to 0°C over 3hrs. It was poured into cold water and extracted with dichloromethane (3 x 50 ml). The combined organics extracts were washed with water,

then brine and dried (Na_2SO_4). Evaporation *in vacuo* gave an oil. Flash silica gel chromatography eluting with ethyl acetate and hexane afforded the desired product as an amber oil (4.3g, 91%).

^{1}H NMR ($CDCl_3$) δ: 1.49 (9H, s), 2.88 (2H, m), 3.67 (2H, m), 4.64 (2H, br s), 7.15 - 7.27 (3H, m).

Description 26

5-Pentafluoroethyl-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline

A mixture of 5-bromo-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (4.0g, 13 mmol), sodium pentafluoropropionate (4.85g, 26 mmol), copper (I) iodide (5.22g, 27.2 mmol), toluene (70 ml) and dimethylformamide (70ml) was heated under argon with Dean-Stark distillation (70ml distillate collected), then heated at reflux for 18h. The mixture was cooled, then poured into a mixture of water (150ml) and .880 ammonia (150ml). Resulting solution was extracted with dichloromethane (4x100ml) and the combined extracts dried (Na_2SO_4) and evaporated *in vacuo* to give a solid. Chromatography on silica with 10 - 50% ether - hexane gradient elution gave the title compound (2.97g, 66%) as a colourless solid.

Mass spectrum (API$^+$): Found 348 (MH^+). $C_{13}H_9F_8NO$ requires 347.

^{1}H NMR ($CDCl_3$) δ: 3.16 (2H, m), 3.83 (2H, m), 4.75 and 4.84 (2H, 2 x s), 7.39 (2H, m), 7.55 (1H, m).

Description 27

6-Pentafluoroethyl-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline

To a mixture of 6-bromo-1,2,3,4-tetrahydroisoquinoline hydrochloride (5.90g, 23.7 mmol), triethylamine (8.3ml; 6g, 59 mmol) and dichloromethane (50ml) at 0°C was added trifluoroacetic anhydride (4.18ml; 6.22g, 29.6 mmol). Mixture was stirred at 20°C for 18h, then partitioned between saturated aqueous $NaHCO_3$ (200ml) and dichloromethane (4x20ml). Combined extracts were dried (Na_2SO_4 and evaporated *in vacuo* to give an oil (7.9g). Treatment of an aliquot of the latter (2.3g, 7.5 mmol) with sodium pentafluoropropionate (2.79g, 15 mmol), copper (I) iodide (3.0g, 15.8 mmol), dimethylformamide (40ml) and toluene (40ml) in a similar manner to Description 26 gave the title compound (1.85g, 71%) as a colourless solid.

Mass spectrum (API$^-$): Found 346 $(M-H)^-$. $C_{13}H_9F_8NO$ requires 347.

^{1}H NMR ($CDCl_3$) δ: 3.04 (2H, m), 3.89 (2H, m), 4.80 and 4.86 (2H, 2 x s), 7.30 (1H, m), 7.45 (2H, m).

Description 28

(4-Bromo-2-methyl)phenylacetonitrile

A mixture of 4-bromo-2-methylbenzyl alcohol (36.6g, 0.18 mol) and triethylamine (33ml; 24g, 0.237 mol) in dichloromethane (300ml) was treated dropwise under argon with methylsulfonyl chloride (16ml; 23.7g, 0.207 mol) with ice cooling. Mixture was stirred at 20°C for 64h then partitioned between saturated aqueous $NaHCO_3$ (1L) and dichloromethane (3x100ml). Combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give an oil (34.3g). The latter was dissolved in dimethylformamide (150ml) and treated with sodium cyanide (8.13g, 0.166 mol). Mixture was stirred vigorously at 20°C for 18h then partitioned between ether (600ml) and water (4x400ml). Organic phase was dried (Na_2SO_4) and evaporated *in vacuo* to give the title compound (30.48g, 78%) as an oil.

^{1}H NMR ($CDCl_3$) δ: 2.35 (3H, s), 3.51 (2H, s), 7.23 (1H, d, J = 8 Hz), 7.38 (2H, m).

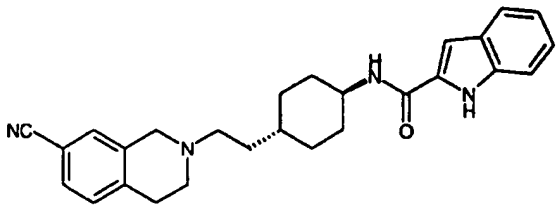
The following compound was prepared in a similar manner to Description 28.

(a) (4-Bromo-3-methyl)phenylacetonitrile

^{1}H NMR ($CDCl_3$) δ: 2.42 (3H, s), 3.68 (2H, s), 7.00 (1H, dd, J = 8, 2 Hz), 7.21 (1H, d, J = 2 Hz), 7.55 (1H, d, J = 8 Hz).

Example 1

***trans*-7-Cyano-2-(2-(1-(4-(2-indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline**



Alternative name: *trans-N*-[4-[2-(7-Cyano-1,2,3,4-tetrahydroisoquinolin-2-yl) ethyl]cyclohexyl]-1*H*-indole-2-carboxamide

A mixture of *cis* and *trans*-2-(2-(1-(4-amino)cyclohexyl)ethyl-7-cyano-1,2,3,4-tetrahydroisoquinoline (350mg, 1.24 mmol), indole-2-carboxylic acid (200mg, 1.24 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (238mg, 1.24 mmol), 1-hydroxybenzotriazole (catalytic amount) and dichloromethane (8ml) was shaken for 16h. Saturated sodium bicarbonate (4ml) was then added and the mixture shaken for 0.25h. Chromatography of the organic layer on silica with 50 - 100% ethyl acetate in hexane

and 0 - 10% methanol in ethyl acetate gradient elution gave the title compound as a yellow solid (90mg, 17%).

Mass spectrum (API$^+$): Found 427 (MH^+). $C_{27}H_{30}N_4O$ requires 426.

^{1}H NMR ($CDCl_3$) δ: 1.08 - 1.36 (4H, m), 1.50 - 1.70 (4H, m), 1.86 (1H, m), 2.12 (2H,. m), 2.55 (2H, m), 2.73 (2H, t, J = 7 Hz), 2.94 (2H, m), 3.60 (2H, s), 3.95 (1H, m), 5.97 (1H, d, J = 8 Hz), 6.81 (1H, m), 7.17 (2H, m), 7.34 (2H, m), 7.42 (2H, t, J = 8 Hz), 7.64 (1H, d, J = 8 Hz), 9.22 (1H, br s).

Example 2

(*E*)-*trans*-7-Cyano-2-(2-(1-(4-(3-(6-indolyl)propenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

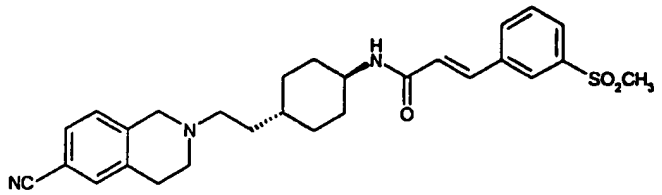
Prepared from (*E*)-3-(6-indolyl)propenoic acid in a similar manner to Example 1. Crystallisation from ethyl acetate gave the title compound (0.19g, 34%) as a yellow solid.

Mass spectrum (API$^+$): Found 453 (MH^+). $C_{29}H_{32}N_4O$ requires 452.

^{1}H NMR (DMSO-d_6) δ: 1.06 (2H, m), 1.21 (2H, m), 1.30 (1H, m), 1.45 (2H, m), 1.86 (4H, m), 2.51 (2H, m), 2.67 (2H, m), 2.89 (2H, m), 3.58 (2H, s), 3.62 (1H, m), 6.46 (1H, d, J = 3 Hz), 6.56 (1H, d, J = 15 Hz), 7.24 (1H, d, J = 8 Hz), 7.32 (1H, d, J = 8 Hz), 7.44 (1H, d, J = 3 Hz), 7.50 (1H, d, J = 15 Hz), 7.56 (4H, m), 7.88 (1H, d, J = 8 Hz), 11.34 (1H, m).

Example 3

***trans*-(*E*)-6-Cyano-2-(2-(1-(4-(3-(3-methylsulfonyl)phenylpropenoyl) amino)cyclohexyl)ethyl-1,2,3,4-tetrahydroisoquinoline**



Alternative name: *trans-(E)-N*-[4-[2-(6-Cyano-1,2,3,4-tetrahydroisoquinolin-2-yl)ethyl]cyclohexyl]-3-[3-(methylsulfonyl)phenyl]-2-propenamide

A mixture of *trans*-2-(2-(1-(4-amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline (0.10g, 0.35 mmol), (*E*)-3-(3-methylsulfonyl)phenylpropenoic acid (0.079g, 0.35 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.067g, 0.35 mmol), 1-hydroxybenzotriazole (catalytic amount) and

dichloromethane (5ml) was treated in a manner to similar to Example 1 to give the title compound (0.065g, 38%) as an off-white solid.

Mass spectrum (API$^+$): Found 492 (MH$^+$). $C_{28}H_{33}N_3O_3S$ requires 491.

^{1}H NMR (DMSO-d_6) δ: 0.97 - 1.38 (5H, m), 1.48 (2H, m), 1.84 (4H, m), 2.52 (2H, m), 2.68 (2H, m), 2.87 (2H, m), 3.29 (3H, s), 3.63 (3H, m), 6.81 (1H, d, J = 16 Hz), 7.31 (1H, d, J = 8 Hz), 7.52 (1H, d, J = 16 Hz), 7.61 (2H, m), 7.72 (1H, t, J = 8 Hz), 7.93 (2H, m), 8.02 (2H, m).

Example 4

***trans*-(*E*)-2-(2-(1-(4-(3-(3-Acetyl)phenylpropenoyl)amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline**

A mixture of *trans*-2-(2-(1-(4-amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline (0.10g, 0.35 mmol), (*E*)-3-(3-acetyl)phenylpropenoic acid (0.066g, 0.35 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.067g, 0.35 mmol), 1-hydroxybenzotriazole (catalytic amount) and dichloromethane (5ml) was treated in a manner similar to Example 1 to give the title compound (0.10g, 63%) as a yellow solid.

Mass spectrum (API$^+$): Found 456 (MH$^+$). $C_{29}H_{33}N_3O_2$ requires 455.

^{1}H NMR (DMSO-d_6) δ: 0.83 - 1.24 (5H, m), 1.33 (2H, m), 1.6 - 1.8 (4H, m), 2.36 (2H, m), 2.49 (3H, s), 2.52 (2H, m), 2.69 (2H, m), 3.48 (3H, m), 6.60 (1H, d, J = 16 Hz), 7.14 (1H, d, J = 8 Hz), 7.35 (1H, d, J = 16 Hz), 7.44 (3H, m), 7.68 (1H, d, J = 8 Hz), 7.82 (1H, d, J = 8 Hz), 7.90 (1H, d, J = 8 Hz), 8.0 (1H, s).

Example 5

***trans*-7-Cyano-2-(2-(1-(4-(3-(4,6-dimethyl)pyrazolo[1,5-a]pyrimidyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline**

A mixture of *trans*-2-(2-(1-(4-amino)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline (0.1g, 0.353 mmol), 4,6-dimethylpyrazolo[1,5-a]pyrimidine-3-carboxylic acid (0.068g, 0.353 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.067g, 0.353 mmol), 1-hydroxybenzotriazole (catalytic amount) and dichloromethane (4ml) was treated in a manner similar to Example 1 to give the title compound (0.096g, 60%) as a pale yellow gum.

Mass spectrum (API$^+$): Found 457 (MH$^+$). $C_{27}H_{32}N_6O$ requires 456.

^{1}H NMR (DMSO-d_6) δ: 0.8 - 1.40 (7H, m), 1.80 (4H, m), 2.37 (3H, s), 2.42 (2H, m), 2.57 (2H, t, J = 5 Hz), 2.71 (3H, s), 2.79 (2H, m), 3.48 (2H, s), 3.61 (1H, m), 6.50 (1H, s), 7.22 (1H, d, J = 5 Hz), 7.47 (2H, m), 8.35 (2H, m).

Example 6

***trans*-7-Cyano-2-(2-(1-(4-(2-(5-fluoro)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline**

A mixture of *trans*-2-(2-(1-(4-amino)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline (0.1g, 0.35 mmol), 5-fluoroindole-2-carboxylic acid (0.07g, 0.35 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.067g, 0.35 mmol), 1-hydroxybenzotriazole (catalytic amount) and dichloromethane (8ml) was treated in a manner similar to Example 1 to give the title compound (0.07g, 45%) as an amber oil.

Mass spectrum (API$^+$): Found 445 (MH^+). $C_{27}H_{29}FN_4O$ requires 444.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.40 (5H, m), 1.45 - 1.55 (2H, m), 1.80 - 1.95 (2H, m), 2.05 - 2.20 (2H, m), 2.56 (2H, m), 2.74 (2H, m), 2.95 (2H, m), 3.62 (2H, s), 3.93 (1H, m), 5.94 (1H, d, J = 8 Hz), 6.75 (1H, m), 7.05 (1H, m), 7.19 (1H, d, J = 8 Hz), 7.22 - 7.42 (4H, m), 9.25 (1H, br s).

Example 7

***trans*-7-Cyano-2-(2-(1-(4-(2-(6-cyano)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline**

A mixture of *trans*-2-(2-(1-(4-amino)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline (0.1g, 0.352 mmol), 6-cyanoindole-2-carboxylic acid (0.066g, 0.355 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.068g, 0.355 mmol), 1-hydroxybenzotriazole (catalytic amount) and dichloromethane (~10ml) was treated in a manner similar to Example 1 to give the title compound (0.096g, 60%) as a colourless solid.

Mass spectrum (API$^+$): Found 452 (MH^+). $C_{28}H_{29}N_5O$ requires 451.

^{1}H NMR ($CDCl_3$) δ: 1.1 - 1.35 (5H, m), 1.51 (2H, m), 1.85 (2H, m), 2.05 (2H, m), 2.55 (2H, m), 2.75 (2H, t, J = 6 Hz), 2.95 (2H, t, J = 6 Hz), 3.58 (2H, s), 3.90 (1H, m), 6.97 (1H, s), 7.19 (1H, d, J = 8 Hz), 7.30 (4H, m), 7.4 (1H, dd, J = 1, 8 Hz), 7.68 (1H, d, J = 8 Hz), 7.78 (1H, s).

Example 8

***trans*-7-Cyano-2-(2-(1-(4-(3,4-methylenedioxy)benzamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline**

Prepared in a similar manner to Example 7, in 43% yield.

Mass spectrum (API$^+$): Found 432 (MH^+). $C_{26}H_{29}N_3O_3$ requires 431.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.40 (5H, m), 1.45 - 1.60 (2H, m), 1.75 - 1.90 (2H, m), 2.05 - 2.16 (2H, m), 2.50 - 2.60 (2H, m), 2.70 - 2.80 (2H, m), 2.90 - 3.00 (2H, m), 3.65 (2H, s), 3.89 (1H, m), 5.77 (1H, d, J = 8 Hz), 6.01 (2H, s), 6.81 (1H, d, J = 10 Hz), 7.15 - 7.50 (5H, m).

The following compounds were prepared in a similar manner to Example 8.

a) ***trans*-7-Cyano-2-(2-(1-(4-(2-indolyl)-*N*-methyl-carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline**

Mass spectrum (API$^+$): Found 441 (MH^+). $C_{28}H_{32}N_4O$ requires 440.

^{1}H NMR ($CDCl_3$+CD_3OD) δ: 1.05 - 1.48 (5H, m), 1.55 (2H, m), 1.90 (4H, m), 2.55 (2H, t, J = 7 Hz), 2.72 (2H, t, J = 7 Hz), 2.94 (2H, t, J = 7 Hz), 3.20 (3H, br s), 3.60 (2H, s), 4.53 (1H, m), 6.78 (1H, br s), 7.05 - 7.48 (6H, m), 7.65 (1H, d, J = 9 Hz), 9.44 (1H, br s).

b) ***trans*-7-Cyano-2-(2-(1-(4-(2-(1-methyl)indolyl)carboxamido)cyclohexyl)ethyl-1,2,3,4-tetrahydroisoquinoline**

Mass spectrum (API$^+$): Found 441 (MH^+). $C_{28}H_{32}N_4O$ requires 440.

^{1}H NMR (DMSO-d_6) δ: 0.96 (2H, m), 1.12 - 1.42 (5H, m), 1.75 (4H, m), 2.41 (2H, m), 2.58 (2H, m), 2.80 (2H, m), 3.49 (2H, m), 3.65 (1H, m), 3.88 (3H, s), 7.00 (2H, m), 7.20 (2H, m), 7.47 (4H, m), 8.17 (1H, d, J = 8 Hz).

c) ***trans*-7-Cyano-2-(2-(1-(4-(2-(5-nitro)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline**

Mass spectrum (API$^+$): Found 472 (MH^+). $C_{27}H_{29}N_5O_3$ requires 471.

^{1}H NMR (DMSO-d_6) δ: 0.98 (2H, m), 1.13 - 1.48 (5H, m), 1.76 (4H, m), 2.40 (2H, m), 2.57 (2H, m), 2.79 (2H, m), 3.48 (2H, m), 3.68 (1H, m), 7.21 (1H, d, J = 8 Hz), 7.34(1H, s), 7.46 (3H, m), 7.96 (1H, dd, J = 9, 2 Hz), 8.41 (1H, d, J = 8 Hz), 8.60 (1H, d, J = 2 Hz), 12.22 (1H, br s).

d) ***trans*-7-Cyano-2-(2-(1-(4-(2-(5-methylsulfonyl)indolyl)carboxamido)**

cyclohexyl)-ethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 505 (MH$^+$). $C_{28}H_{32}N_4O_3S$ requires 504.

^{1}H NMR (DMSO-d_6) δ: 0.93 (2H, m), 1.09 - 1.38 (5H, m), 1.71 (4H, m), 2.34 (2H, m), 2.52 (2H, m), 2.74 (2H, m), 3.04 (3H, s), 3.44 (2H, s), 3.64 (1H, m), 7.20 (2H, m), 7.48 (3H, m), 8.11 (2H, d, J = 2 Hz), 8.32 (1H, d, J = 8 Hz), 12.02 (1H, br s).

e) *trans*-7-Cyano-2-(2-(1-(4-(3-isoquinolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 439 (MH$^+$). $C_{28}H_{30}N_4O$ requires 438.

^{1}H NMR ($CDCl_3$) δ: 1.11 - 1.44 (4H, m), 1.56 (2H, m), 1.88 (2H, m), 2.01 (1H, m), 2.14 (2H, m), 2.58 (2H, m), 2.76 (2H, t, J = 7 Hz), 2.97 (2H, m), 3.64 (2H, s), 3.99 (1H, m), 7.19 (1H, d, J = 8 Hz), 7.32 (1H, s), 7.39 (1H, d, J = 8 Hz), 7.73 (2H, m), 8.04 (3H, m), 8.62 (1H, s), 9.15 (1H, s).

f) *trans*-7-Cyano-2-(2-(1-(4-(2-(5-methoxy)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 457 (MH$^+$). $C_{28}H_{32}N_4O_2$ requires 456.

^{1}H NMR ($CDCl_3$) δ: 1.15 - 1.40 (5H, m), 1.50 - 1.58 (2H, m), 1.80 - 1.90 (2H, m), 2.10 - 2.20 (2H, m), 2.50 - 2.60 (2H, m), 2.70 - 2.80 (2H, m), 2.90 - 3.00 (2H, m), 3.49 (2H, s), 3.85 (3H, s), 3.95 (1H, m), 5.90 (1H, d, J = 8 Hz), 6.70 (1H, d, J = 2 Hz), 6.96 (1H, dd, J = 2, 8 Hz), 7.05 (1H, d, J = 2 Hz), 7.20 (1H, d, J = 7.5 Hz), 7.30 - 7.37 (2H, m), 7.40 - 7.46 (1H, m), 9.08 (1H, br s).

g) *trans*-2-(2-(1-(4-(4-(4-Acetyl)phenyl)benzoyl)aminocyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 506 (MH$^+$). $C_{33}H_{35}N_3O_2$ requires 505.

^{1}H NMR (DMSO-d_6) δ: 1.10 (2H, m), 1.24 - 1.54 (5H, m), 1.87 (4H, m), 2.52 (2H, m), 2.65 (3H, s), 2.68 (2H, m), 2.87 (2H, m), 3.64 (2H, s), 3.79 (1H, m), 7.31 (1H, d, J = 8Hz), 7.59 (2H, m), 7.91 (4H, m), 8.00 (2H, d, J = 8Hz) 8.08 (2H, d, J = 8Hz), 8.32 (1H, d, J = 8Hz).

h) *trans*-7-Cyano-2-(2-(1-(4-(2-(7-nitro)indolyl)carboxamido)cyclohexyl)ethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 472 (MH$^+$). $C_{27}H_{29}N_5O_3$ requires 471.

^{1}H NMR (DMSO-d_6) δ: 1.07 (2H, m), 1.32 (3H, m), 1.60 (2H, m), 1.79 (2H, m), 1.90 (2H, m), 2.80 - 3.25 (6H, m), 3.30 (2H, s), 3.23 (1H, m), 7.28 (1H, t, J = 9 Hz), 7.35 (2H, m), 7.65 (2H, m), 8.15 (2H, m), 8.29 (1H, d, J = 9 Hz), 11.34 (1H, br s).

i) *trans*-7-Cyano-2-(2-(1-(4-(2-(5-methyl)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 441 (MH^+). $C_{28}H_{32}N_4O$ requires 440.

^{1}H NMR ($CDCl_3$+CD_3OD) δ: 1.06 - 1.48 (5H, m), 1.57 (2H, m), 1.89 (2H, m), 2.07 (2H, m), 2.43 (3H, s), 2.61 (2H, m), 2.84 (2H, t, J = 7 Hz), 3.00 (2H, m), 3.66 (2H, s), 3.90 (1H, m), 6.94 (1H, s), 7.11 (1H, d, J = 9 Hz), 7.15 - 7.50 (6H, m).

j) *trans*-7-Cyano-2-(2-(1-(4-(2-(1*H*)-pyrrolo[3,2-b]pyridyl)carboxamido) cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 428 (MH^+). $C_{26}H_{29}N_5O$ requires 427.

^{1}H NMR ($CDCl_3$+CD_3OD) δ: 1.06 - 1.65 (7H, m), 1.90 (2H, m), 2.07 (2H, m), 2.60 (2H, m), 2.75 (2H, m), 2.98 (2H, m), 3.65 (2H, s), 3.94 (1H, m), 7.10 (1H, s), 7.24 (2H, m), 7.30 (1H, s), 7.36 (1H, s), 7.44 (1H, d, J = 9 Hz), 7.83 (1H, d, J = 9 Hz), 8.44 (1H, d, J = 5 Hz).

k) *trans*-7-Cyano-2-(2-(1-(4-(3-pyrazolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 378 (MH^+). $C_{22}H_{27}N_5O$ requires 377.

^{1}H NMR ($CDCl_3$+CD_3OD) δ: 1.04 - 1.45 (5H, m), 1.54 (2H, m), 1.85 (2H, m), 2.05 (2H, m), 2.55 (2H, m), 2.75 (2H, m), 2.98 (2H, m), 3.63 (2H, s), 3.85 (1H, m), 6.49 (1H, m), 7.22 (1H, d, J = 9 Hz), 7.34 (1H, s), 7.43 (1H, d, J = 9 Hz), 7.93 (2H, br s).

l) *trans*-7-Cyano-2-(2-(1-(4-(6-(1-methyl)benzimidazolyl)carboxamido)cyclohexyl)-ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 442 (MH^+). $C_{27}H_{31}N_5O$ requires 441.

^{1}H NMR ($CDCl_3$) δ: 1.03 - 1.47 (5H, m), 1.55 (2H, m), 1.87 (2H, m), 2.16 (2H, m), 2.56 (2H, m), 2.75 (2H, t, J = 7 Hz), 2.96 (2H, m), 3.64 (2H, s), 3.91 (3H, s), 4.00 (1H, m), 6.04 (1H, d, J = 10 Hz), 7.18 (1H, d, J = 8 Hz), 7.34 (1H, s), 7.41 (1H, d, J = 8 Hz), 7.56 (1H, dd, J = 9,2 Hz), 7.79 (1H, d, J = 9 Hz), 7.96 (1H, s), 8.03 (1H, d, J = 2 Hz).

m) *trans*-7-Cyano-2-(2-(1-(4-(5-(1,2-dihydro)benzofuranyl)carboxamido)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 430 (MH$^+$). $C_{27}H_{31}N_3O_2$ requires 429.

^{1}H NMR ($CDCl_3$) δ: 1.05 - 1.45 (5H, m), 1.53 (2H, m), 1.85 (2H, m), 2.09 (2H, m), 2.54 (2H, m), 2.72 (2H, t, J = 7 Hz), 2.95 (2H, m), 3.22 (2H, t, J = 10 Hz), 3.62 (2H, s), 3.90 (1H, m), 4.63 (2H, t, J = 10 Hz), 5.83 (1H, d, J = 10 Hz), 6.26 (1H, d, J = 9 Hz), 7.20 (1H, d, J = 9 Hz), 7.33 (1H, s), 7.39 (1H, d, J = 9 Hz), 7.52 (1H, dd, J = 9, 2 Hz, 7.66 (1H, d, J = 2 Hz).

n) *trans*-7-Cyano-2-(2-(1-(4-(2-thieno[3,2-b]thiophenyl)carboxamido)cyclohexyl)ethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 450 (MH$^+$). $C_{25}H_{27}N_3OS_2$ requires 449.

^{1}H NMR ($CDCl_3$) δ: 1.03 - 1.47 (5H, m), 1.55 (2H, m), 1.85 (2H, m), 2.13 (2H, m), 2.53 (2H, m), 2.75 (2H, m), 2.95 (2H, m), 3.63 (2H, s), 3.94 (1H, m), 5.85 (1H, m), 7.12 - 7.48 (4H, m), 7.51 (1H, d, J = 5 Hz), 7.70 (1H, s).

o) *trans*-7-Cyano-2-(2-(1-(4-(4-indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 427 (MH$^+$). $C_{27}H_{30}N_4O$ requires 426.

^{1}H NMR ($CDCl_3$) δ: 1.15 - 1.21 (5H, m), 1.55 (2H, m), 1.85 (2H, m), 2.2 (2H, m), 2.55 (2H, t, J = 6 Hz), 2.75 (2H, t, J = 6 Hz), 2.95 (2H, m), 3.62 (2H, s), 4.05 (1H, m), 6.05 (1H, d, J = 8 Hz), 6.9 (1H, m), 7.15 - 7.22 (1H, m), 7.25 (1H, s), 7.32 (2H, m), 7.40 (1H, m), 7.50 (2H, m), 8.40 (1H, br s).

p) *trans*-7-Cyano-2-(2-(1-(4-(2-(6-methoxy)indolyl)carboxamido)cyclohexyl)ethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 457 (MH$^+$). $C_{28}H_{32}N_4O_2$ requires 456.

^{1}H NMR ($CDCl_3$) δ: 1.15 - 1.30 (5H, m), 1.55 (2H, m), 1.85 (2H, m), 2.10 (2H, m), 2.55 (2H, m), 2.75 (2H, t, J = 6 Hz), 2.94 (2H, t, J = 6 Hz), 3.62 (2H, s), 3.85 (3H, s), 3.92 (1H, m), 5.85 (1H, d, J = 8 Hz), 6.70 (1H, d, J = 1 Hz), 6.80 (1H, dd, J = 8, 1 Hz), 6.85 (1H, br s), 7.2 (1H, d, J = 8 Hz), 7.30 (1H, s), 7.40 (1H, d, J = 8 Hz), 7.50 (1H, d, J = 8 Hz), 8.90 (1H, s).

q) *trans*-7-Cyano-2-(2-(1-(4-(2-(6-chloro)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 461 (MH$^+$). $C_{27}H_{29}{}^{35}ClN_4O$ requires 460.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.32 (5H, m), 1.48 - 1.60 (2H, m), 1.85 (2H, m), 2.08 (2H, m), 2.60 (2H, m), 2.74 (2H, m), 2.95 (2H, m), 3.62 (2H, s), 3.88 (1H, s), 6.62 (1H, m), 6.85 (1H, s), 7.05 (1H, dd, J = 8, 1 Hz), 7.20 (1H, d, J = 8 Hz), 7.30 (1H, m), 7.40 (2H, m), 7.52 (1H, d, J = 8 Hz), 10.22 (1H, s).

r) *trans*-7-Cyano-2-(2-(1-(4-(2-(6-fluoro)indolyl)carboxamido)cyclohexyl)ethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 445 (MH$^+$). $C_{27}H_{29}FN_4O$ requires 444.

^{1}H NMR ($CDCl_3$) δ: 1.09 - 1.35 (5H, m), 1.50 - 1.60 (2H, m), 1.88 (2H, m), 2.09 (2H, m), 2.54 - 2.62 (2H, m), 2.76 (2H, t, J = 6 Hz), 2.96 (2H, t, J = 6 Hz), 3.63 (2H, s), 3.88 (1H, m), 6.66 (1H, d, J = 8 Hz), 6.90 (2H, m), 7.10 (1H, dd, J = 8, 2 Hz), 7.22 (1H, d, J = 8 Hz), 7.32 (2H, m), 7.42 (1H, dd, J = 8, 2 Hz), 7.5 (1H, m).

s) *trans*-7-Cyano-2-(2-(1-(4-(2-(6-methyl)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 441 (MH$^+$). $C_{28}H_{32}N_4O$ requires 440.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.35 (5H, m), 1.53 (2H, m), 1.87 (2H, m),2.09 (2H, m), 2.46 (3H, s), 2.59 (2H, m), 2.78 (2H, m), 3.0 (2H, m), 3.66 (2H, s), 3.95 (1H, s), 6.95 (2H, m), 7.24 (2H, m), 7.34 (1H, m), 7.45 (2H, m), 7.51 (1H, m), 7.98 (1H, m).

t) *trans*-2-(2-(1-(4-(2-(5-Chloro)benzofuranyl)carboxamido)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 462 (MH$^+$). $C_{27}H_{28}{}^{35}ClN_3O_2$ requires 461.

^{1}H NMR (DMSO-d_6) δ: 0.91 - 1.36 (7H, m), 1.72 4H, m), 2.37 (2H, m), 2.56 (2H, t, J = 6 Hz), 2.76 (2H, t, J = 6 Hz), 3.47 (2H, s), 3.63 (1H, m), 7.21 (1H, d, J = 8 Hz), 7.36 (1H, dd, J = 8, 2 Hz), 7.42 (1H, s), 7.44 (2H, m), 7.60 (1H, d, J = 8 Hz), 7.77 (1H, d, J = 2 Hz), 8.48 (1H, d, J = 8 Hz).

u) *trans*-2-(2-(1-(4-(2-(3-Amino)naphthyl)carboxamido)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 453 (MH$^+$). $C_{29}H_{32}N_4O$ requires 452.

^{1}H NMR (DMSO-d_6) δ: 0.8 - 1.40 (7H, m), 1.65 (4H, m), 2.28 (2H, m), 2.45 (2H, t, J = 6 Hz), 2.67 (2H, t, J = 6 Hz), 3.36 (2H, s), 3.55 (1H, m), 5.83 (2H, br s), 6.73 (1H, s),

6.92 (1H, m), 7.10 (2H, m), 7.29 (1H, d, J = 8 Hz), 7.32 (2H, m), 7.48 (1H, d, J = 8 Hz), 7.75 (1H, s), 8.14 (1H, d, J = 8 Hz).

v) *trans*-7-Cyano-2-(2-(1-(4-(2-thienyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 394 (MH$^+$). $C_{23}H_{27}N_3OS$ requires 393.

^{1}H NMR (DMSO-d_6) δ: 1.00 - 1.60 (7H, m), 1.87 (4H, m), 2.52 (2H, m), 2.71 (2H, t, J = 6 Hz), 2.91 (2H, t, J = 6 Hz), 3.62 (2H, s), 3.73 (1H, m), 7.17 (1H, m), 7.35 (1H, d, J = 8 Hz), 7.62 (2H, m), 7.77 (1H, m), 7.83 (1H, m), 8.26 (1H, d, J = 7 Hz).

w) *trans*-7-Cyano-2-(2-(1-(4-(2-naphthyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 438 (MH$^+$). $C_{29}H_{31}N_3O$ requires 437.

^{1}H NMR (DMSO-d_6) δ: 1.10 - 1.70 (7H, m), 2.07 (4H, m), 2.63 (2H, m), 2.82 (2H, t, J = 6 Hz), 3.30 (2H, t, J = 6 Hz), 3.73 (2H, s), 3.97 (1H, m), 7.64 (1H, d, J = 8 Hz), 7.75 (4H, m), 8.10 (4H, m), 8.53 (1H, d, J = 8 Hz), 8.58 (1H, s).

x) *trans*-7-Cyano-2-(2-(1-(4-(3-indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 427 (MH$^+$). $C_{27}H_{30}N_4O$ requires 426.

^{1}H NMR (DMSO-d_6) δ: 0.9 - 1.55 (7H, m), 1.82 (4H, m), 2.46 (2H, m), 2.64 (2H, t, J = 6 Hz), 2.84 (2H, t, J = 6 Hz), 3.55 (2H, s), 3.71 (1H, m), 7.08 (2H, m), 7.28 (1H, d, J = 8 Hz), 7.37 (1H, m), 7.56 (3H, m), 8.00 (1H, d, J = 2 Hz), 8.11 (1H, m), 11.5 (1H, br s).

y) *trans*-(*E*)-7-Cyano-2-(2-(1-(4-(3-phenylpropenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 414 (MH$^+$). $C_{27}H_{31}N_3O$ requires 413.

^{1}H NMR (DMSO-d_6) δ: 1.00 - 1.60 (7H, m), 1.90 (4H, m), 2.54 (2H, m), 2.74 (2H, t, J = 6 Hz), 2.95 (2H, t, J = 6 Hz), 3.65 (2H, s), 3.67 (1H, m), 6.69 (1H, d, J = 16 Hz), 7.38 (1H, d, J = 8 Hz), 7.46 (4H, m), 7.65 (4H, m), 8.07 (1H, d, J = 8 Hz).

z) *trans*-6-Cyano-2-(2-(1-(4-(1-naphthyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 438 (MH$^+$). $C_{29}H_{31}N_3O$ requires 437.

^{1}H NMR (DMSO-d_6) δ: 1.08 (2H, m), 1.30 (3H, m), 1.47 (2H, m), 1.83 (2H, m), 1.97 (2H, m), 2.52 (2H, m), 2.67 (2H, m), 2.86 (2H, m), 3.63 (2H, s), 3.81 (1H, m), 7.30 (1H, d, J = 8 Hz), 7.54 (6H, m), 7.99 (2H, m), 8.17 (1H, m), 8.42 (1H, d, J = 8 Hz).

a1) *trans*-2-(2-(1-(4-(2-Benzo[b]thienyl)carboxamido)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 444 (MH^+). $C_{27}H_{29}N_3OS$ requires 443.

^{1}H NMR (DMSO-d_6) δ: 0.85 (2H, m), 0.99 - 1.33 (5H, m), 1.66 (4H, m), 2.28 (2H, m), 2.47 (2H, m), 2.66 (2H, m), 3.43 (2H, s), 3.64 (1H, m), 7.09 (1H, d, J = 8 Hz), 7.26 (2H, m), 7.39 (2H, m), 7.74 (1H, m), 7.84 (1H, m), 7.94 (1H, s), 8.35 (1H, d, J = 8 Hz).

b1) *trans*-6-Cyano-2-(2-(1-(4-(5-indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 427 (MH^+). $C_{27}H_{30}N_4O$ requires 426.

^{1}H NMR (DMSO-d_6) δ: 0.85 (2H, m), 1.01 - 1.29 (5H, m), 1.58 (4H, m), 2.27 (2H, m), 2.44 (2H, m), 2.63 (2H, m), 3.40 (2H, s), 3.54 (1H, m), 6.30 (1H, d, J = 3 Hz), 7.08 (1H, d, J = 8 Hz), 7.18 (2H, m), 7.38 (3H, m), 7.82 (1H, d, J = 8 Hz), 7.90 (1H, s), 11.11 (1H, br s).

c1) *trans*-6-Cyano-2-(2-(1-(4-(6-indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 427 (MH^+). $C_{27}H_{30}N_4O$ requires 426.

^{1}H NMR (DMSO-d_6) δ: 0.87 (2H, m), 1.02 - 1.31 (5H, m), 1.63 (4H, m), 2.27 (2H, m), 2.45 (2H, m), 2.64 (2H, m), 3.41 (2H, s), 3.57 (1H, m), 6.26 (1H, d, J = 3 Hz), 7.08 (1H, d, J = 8 Hz), 7.33 (5H, m), 7.73 (1H, s), 7.88 (1H, d, J = 8 Hz), 11.16 (1H, br s).

d1) *trans*-6-Cyano-2-(2-(1-(4-(2-thieno[3,2-b]thiophenyl)carboxamido)cyclohexyl)-ethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 450 (MH^+). $C_{25}H_{27}N_3OS_2$ requires 449.

^{1}H NMR (DMSO-d_6) δ: 0.88 (2H, m), 1.06 - 1.34 (5H, m), 1.67 (4H, m), 2.34 (2H, m), 2.49 (2H, m), 2.68 (2H, m), 3.45 (2H, s), 2.56 (1H, m), 7.12 (1H, d, J = 8 Hz), 7.32 (1H, d, J = 5 Hz), 7.41 (2H, m), 7.67 (1H, d, J = 5 Hz), 7.95 (1H, s), 8.20 (1H, d, J = 8 Hz).

e1) *trans*-6-Cyano-2-(2-(1-(4-(3,4-methylenedioxy)benzamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 432 (MH$^+$). $C_{26}H_{29}N_3O_3$ requires 431.

^{1}H NMR (DMSO-d_6) δ: 1.00 (2H, m), 1.08 - 1.47 (5H, m), 1.78 (4H, m), 2.47 (2H, m), 2.62 (2H, m), 2.81 (2H, m), 3.57 (2H, s), 3.68 (1H, m), 6.05 (2H, s), 6.94 (1H, d, J = 8 Hz), 7.25 (1H, d, J = 8 Hz), 7.38 (2H, m), 7.56 (2H, m), 7.99 (1H, d, J = 8 Hz).

f1) *trans*-2-(2-(1-(4-(2-Benzofuranyl)carboxamido)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 428 (MH$^+$). $C_{27}H_{29}N_3O_2$ requires 427.

^{1}H NMR (DMSO-d_6) δ: 0.84 (2H, m), 1.02 - 1.32 (5H, m), 1.61 (4H, m), 2.30 (2H, m), 2.46 (2H, m), 2.63 (2H, m), 3.42 (2H, s), 3.55 (1H, m), 7.11 (2H, m), 7.26 (1H, m), 7.39 (4H, m), 7.56 (1H, d, J = 8 Hz), 8.30 (1H, d, J = 8 Hz).

g1) *trans*-(E)-6-Cyano-2-(2-(1-(4-(3-(5-(1,2-dihydro-2-oxo)-(3*H*)-indolyl)propenoyl)amino)cyclohexyl)ethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 469 (MH$^+$). $C_{29}H_{32}N_4O_2$ requires 468.

^{1}H NMR (DMSO-d_6) δ: 0.83 - 1.18 (5H, m), 1.33 (2H, m), 1.68 (4H, m), 2.38 (2H, m), 2.53 (2H, m), 2.73 (2H, m), 3.40 (2H, s), 3.49 (3H, m), 6.33 (1H, d, J = 16 Hz), 6.66 (2H, m), 7.21 (4H, m), 7.48 (2H, m), 7.75 (1H, m).

h1) *trans*-(*E*)-6-Cyano-2-(2-(1-(4-(3-phenylpropenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 414 (MH$^+$). $C_{27}H_{31}N_3O$ requires 413.

^{1}H NMR (DMSO-d_6) δ: 0.83 - 1.22 (5H, m), 1.34 (2H, m), 1.70 (4H, m), 2.38 (2H, m), 2.54 (2H, m), 2.73 (2H, m), 3.50 (3H, m), 6.49 (1H, d, J = 16 Hz), 7.17 (1H, d, J = 8 Hz), 7.29 (4H, m), 7.45 (4H; m), 7.88 (1H, d, J = 8 Hz).

i1) *trans*-(*E*)-6-Cyano-2-(2-(1-(4-(3-(4-ethylsulfonyl)phenylpropenoyl)-amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 492 (MH$^+$). $C_{28}H_{33}N_3O_3S$ requires 491.

^{1}H NMR (DMSO-d_6) δ: 0.86 - 1.26 (5H, m), 1.37 (2H, m), 1.73 (4H, m), 2.40 (2H, m), 2.56 (2H, m), 2.76 (2H, m), 3.16 (3H, s), 3.52 (3H, m), 6.68 (1H, d, J = 16 Hz), 7.20 (1H, d, J = 8 Hz), 7.40 (1H, d, J = 16 Hz), 7.49 (2H, m), 7.72 (2H, d, J = 8 Hz), 7.87 (2H, d, J = 8 Hz), 8.04 (1H, d, J = 8 Hz).

j1) ***trans*-(*E*)-2-(2-(1-(4-(3-(4-Acetyl)phenylpropenoyl)amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline**

Mass spectrum (API$^+$): Found 456 (MH$^+$). $C_{29}H_{33}N_3O_2$ requires 455.

^{1}H NMR (DMSO-d_6) δ: 0.90 - 1.28 (5H, m), 1.39 (2H, m), 1.76 (4H, m), 2.42 (2H, m), 2.53 (3H, s), 2.59 (2H, m), 2.78 (2H, m), 3.54 (3H, m), 6.67 (1H, d, J = 16 Hz), 7.22 (1H, d, J = 8 Hz), 7.40 (1H, d, J = 16 Hz), 7.52 (2H, m), 7.62 (2H, d, J = 8 Hz), 7.92 (2H, d, J = 8 Hz), 8.01 (1H, d, J = 8 Hz).

k1) ***trans*-(*E*)-6-Cyano-2-(2-(1-(4-(3-(3,4-methylenedioxy)phenylpropenoyl)-amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline**

Mass spectrum (API$^+$): Found 458 (MH$^+$). $C_{28}H_{31}N_3O_3$ requires 457.

^{1}H NMR (DMSO-d_6) δ: 0.94 - 1.26 (5H, m), 1.44 (2H, m), 1.81 (4H, m), 2.49 (2H, m), 2.65 (2H, m), 2.85 (2H, m), 3.61 (3H, m), 6.07 (2H, s), 6.44 (1H, d, J = 16 Hz), 6.95 (1H, d, J = 8 Hz), 7.09 (2H, m), 7.31 (2H, m), 7.58 (2H, m), 7.87 (1H, d, J = 8 Hz).

l1) ***trans*-(*E*)-6-Cyano-2-(2-(1-(4-(3-(3-thienyl)propenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline**

Mass spectrum (API$^+$): Found 420 (MH$^+$). $C_{25}H_{29}N_3OS$ requires 419.

^{1}H NMR (DMSO-d_6) δ: 0.92 - 1.25 (5H, m), 1.42 (2H, m), 1.80 (4H, m), 2.48 (2H, m), 2.64 (2H, m), 2.83 (2H, m), 3.59 (3H, m), 6.40 (1H, d, J = 16 Hz), 7.29 (2H, m), 7.39 (1H, d, J = 16 Hz), 7.50 (3H, m), 7.77 (1H, d, J = 3 Hz), 7.91 (1H, d, J = 8 Hz).

m1) ***trans*-(*E*)-6-Cyano-2-(2-(1-(4-(3-(2-thienyl)propenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline**

Mass spectrum (API$^+$): Found 420 (MH$^+$). $C_{25}H_{29}N_3OS$ requires 419.

^{1}H NMR (DMSO-d_6) δ: 0.83 - 1.16 (5H, m), 1.31 (2H, m), 1.69 (4H, m), 2.37 (2H, m), 2.53 (2H, m), 2.73 (2H, m), 3.49 (3H, m), 6.24 (1H, d, J = 16 Hz), 6.99 (1H, m), 7.17 (1H, d, J = 8 Hz), 7.25 (1H, d, J = 3 Hz), 7.44 (4H, m), 7.87 (1H, d, J = 8 Hz).

n1) ***trans*-(*E*)-2-(2-(1-(4-(3-(2-Acetyl)phenylpropenoyl)amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline**

Mass spectrum (API$^+$): Found 471 (MH$^+$). $C_{29}H_{34}N_4O_2$ requires 470.

^{1}H NMR (DMSO-d_6) δ: 0.79 - 1.14 (5H, m), 1.30 (2H, m), 1.64 (4H, m), 1.92 (3H, s), 2.31 (2H, m), 2.50 (2H, m), 2.69 (2H, m), 3.45 (3H, m) 6.39 (1H, d, J = 16 Hz), 7.03 - 7.30 (4H, m), 7.42 (4H, m), 7.87 (1H, d, J = 8 Hz), 9.61 (1H, s).

o1) *trans*-(*E*)-2-(2-(1-(4-(3-(4-Acetyl)phenylpropenoyl)amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 471 (MH^+). $C_{29}H_{34}N_4O_2$ requires 470.

^{1}H NMR (DMSO-d_6) δ: 0.82 (5H, m), 1.33 (2H, m), 1.69 (4H, m), 1.95 (3H, s), 2.37 (2H, m), 2.54 (2H, m), 2.73 (2H, m), 3.49 (3H, m), 6.37 (1H, d, J = 16 Hz), 7.20 (2H, m), 7.36 (2H, m), 7.48 (4H, m), 7.83 (1H, d, J = 8 Hz), 10.02 (1H, s).

p1) *trans*-(*E*)-6-Cyano-2-(2-(1-(4-(3-(4-methoxy)phenylpropenoyl)amino)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 444 (MH^+). $C_{28}H_{33}N_3O_2$ requires 443.

^{1}H NMR (DMSO-d_6) δ: 1.12 - 1.43 (5H, m), 1.61 (2H, m), 1.98 (4H, m), 2.67 (2H, m), 2.71 (2H, m), 3.02 (2H, m), 3.78 (3H, m), 3.96 (3H, s), 6.62 (1H, d, J = 16 Hz), 7.14 (2H, d, J = 8 Hz), 7.50 (2H, m), 7.67 (2H, d, J = 8 Hz), 7.75 (2H, m), 8.07 (1H, d, J = 8 Hz).

q1) *trans*-(*E*)-2-(2-(1-(4-(3-(4-Chloro)phenylpropenoyl)amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 448 (MH^+). $C_{27}H_{30}{}^{35}ClN_3O$ requires 447.

^{1}H NMR (DMSO-d_6) δ: 0.76 - 1.09 (5H, m), 1.26 (2H, m), 1.63 (4H, m), 2.30 (2H, m), 2.46 (2H, m), 2.66 (2H, m), 3.42 (3H, m), 6.43 (1H, d, J = 16 Hz), 7.09 (1H, d, J = 8 Hz), 7.2 (1H, d, J = 16 Hz), 7.29 (2H, m), 7.37 (4H, m), 7.82 (1H, d, J = 8 Hz).

r1) *trans*-(*E*)-6-Cyano-2-(2-(1-(4-(3-(3-methylaminocarbonyl)phenylpropenoyl)-amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 471 (MH^+). $C_{29}H_{34}N_4O_2$ requires 470.

^{1}H NMR (DMSO-d_6) δ: 1.09 - 1.38 (5H, m), 1.58 (2H, m), 1.96 (4H, m), 2.64 (2H, m), 2.79 (2H, m), 2.97 (5H, m), 3.75 (3H, m), 6.85 (1H, d, J = 16 Hz), 7.43 (1H, d, J = 8 Hz), 7.58 (1H, d, J = 16 Hz), 7.69 (3H, m), 7.82 (1H, m), 7.95 (1H, m), 8.20 (2H, m), 8.71 (1H, m).

s1) *trans*-(*E*)-6-Cyano-2-(2-(1-(4-(3-(4-methylaminocarbonyl)phenylpropenoyl)-amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 471 (MH^+). $C_{29}H_{34}N_4O_2$ requires 470.

^{1}H NMR (DMSO-d_6) δ: 0.79 - 1.10 (5H, m), 1.25 (2H, m), 1.62 (4H, m), 2.28 (2H, m), 2.45 (2H, m), 2.61 (5H, m), 3.40 (3H, m), 6.49 (1H, d, J = 16 Hz), 7.08 (1H, d, J = 8 Hz), 7.23 (1H, d, J = 16 Hz), 7.40 (4H, m), 7.67 (2H, d, J = 8 Hz), 7.85 (1H, m), 8.29 (1H, m).

t1) *trans*-7-Cyano-2-(2-(1-(4-(6-indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 427.2 (MH^+). $C_{27}H_{30}N_4O$ requires 426.

^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ: 1.00 - 1.40 (5H, m), 1.40 - 1.60 (2H, m), 1.85 (2H, m), 2.06 (2H, m), 2.58 (2H, m), 2.74 (2H, t, J = 6 Hz), 2.95 (2H, m), 3.62 (2H, s), 3.91 (1H, m), 6.49 (1H, s), 6.95 (1H, d, J = 5.5 Hz), 7.22 (1H, d, J = 8 Hz), 7.31 (2H, m), 7.40 (1H, d, J = 8Hz), 7.47 (1H, d, J = 8 Hz), 7.58 (1H, d, J = 8 Hz), 7.99 (1H, s), 10.64 (1H, s).

u1) *trans*-2-(2-(1-(4-(2-(5-Chloro)indolyl)carboxamido)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 461.2 (MH^+). $C_{27}H_{29}N_4{}^{35}ClO$ requires 460.

^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ: 1.12 (2H, m), 1.37 (3H, m), 1.51 (2H, m), 1.88 (2H, m), 2.01 (2H, m), 2.58 (2H, m, partially obscured by DMSO), 2.75 (2H, t, J = 6 Hz), 2.96 (2H, t, J = 6 Hz), 3.63 (2H, s), 3.91 (1H, m), 7.06 (1H, d, J = 2 Hz), 7.11 (1H, dd, J = 9 and 2 Hz), 7.24 (1H, d, J = 8 Hz), 7.40 (2H, m), 7.55 (1H, d, J = 2 Hz), 7.76 (2H, m).

v1) *trans*-7-Cyano-2-(2-(1-(4-(3-thienyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 394 (MH^+). $C_{23}H_{27}N_3OS$ requires 393.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.40 (5H, m), 1.53 (2H, m), 1.86 (2H, m), 2.08 (2H, m), 2.55 (2H, t, J = 8 Hz), 2.73 (2H, J = 6 Hz), 2.95 (2H, t, J = 6 Hz), 3.62 (2H, s), 3.92 (1H, m), 5.73 (1H, d, J = 8 Hz), 7.19 (1H, d, J = 8 Hz), 7.34 (3H, m), 7.40 (1H, dd, J = 8, 1.5 Hz), 7.82 (1H, dd, J = 3, 1.5 Hz).

w1) *trans*-2-(2-(1-(4-(2-(3-Chloro)benzo[b]thienyl)carboxamido)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 478 (MH^+). $C_{27}H_{28}N_3{}^{35}ClOS$ requires 477.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.40 (5H, m), 1.5 - 1.7 (2H, m), 1.87 (2H, m), 2.18 (2H, m), 2.56 (2H, m), 2.74 (2H, t, J = 6 Hz), 2.94 (2H, t, J = 6 Hz), 3.62 (2H, s), 3.96 (1H, m), 6.97 (1H, d, J = 8 Hz), 7.19 (1H, d, J = 8 Hz), 7.33 (1H, s), 7.40 (1H, d, J = 8 Hz), 7.50 (2H, m), 7.85 (2H, m).

x1) *trans*-7-Cyano-2-(2-(1-(4-(6-quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 439 (MH^+). $C_{28}H_{30}N_4O$ requires 438.

^{1}H NMR (DMSO-d_6) δ: 1.10 - 1.30 (2H, m), 1.30 - 1.60 (5H, m), 1.80 - 2.00 (4H, m), 2.60 (2H, m), 2.75 (2H, m), 2.96 (2H, m), 3.66 (2H, s), 3.89 (1H, m), 7.39 (1H, d, J = 8 Hz), 7.6 (3H, m), 8.15 (1H, d, J = 8 Hz), 8.26 (1H, dd, J = 8, 2 Hz), 8.6 (3H, m), 9.1 (1H, m).

y1) *trans*-(*E*)-7-Cyano-2-(2-(1-(4-(3-(2-(3,4-dimethyl)thieno[2,3-b]thiophenyl)propenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 504 (MH^+). $C_{29}H_{33}N_3OS_2$ requires 503.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.40 (5H, m), 1.45 - 1.55 (2H, m), 1.84 (2H, m), 2.04 (2H, m), 2.48 (3H, s), 2.54 (3H, s), 2.40 - 2.60 (2H, m), 2.73 (2H, t, J = 6 Hz), 2.93 (2H, t, J = 6 Hz), 3.61 (2H, s), 3.86 (1H, m), 5.36 (1H, d, J = 8 Hz), 6.04 (1H, d, J = 15 Hz), 6.87 (1H, s), 7.19 (1H, d, J = 8 Hz), 7.33 (1H, s), 7.39 (1H, d, J = 8 Hz), 7.88 (1H, d, J = 15 Hz).

z1) *trans*-(*E*)-7-Cyano-2-(2-(1-(4-(3-(3-methylaminocarbonyl)phenylpropenoyl)-amino)cyclohexyl)ethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 471 (MH^+). $C_{29}H_{34}N_4O_2$ requires 470.

^{1}H NMR ($CDCl_3$) δ: 1.20 (5H, m), 1.50 (2H, m), 1.70 (2H, m), 2.04 (2H, m), 2.51 (2H, m), 2.73 (2H, t, J = 6 Hz), 2.95 (2H, t, J = 6 Hz), 3.02 (3H, d, J = 5 Hz), 3.61 (2H, s), 3.86 (1H, m), 5.75 (1H, d, J = 8 Hz), 6.41 (1H, d, J = 16 Hz), 6.44 (1H, m), 7.18 (1H, d, J = 8 Hz), 7.40 (3H, m), 7.55 (2H, m), 7.67 (1H, d, J = 8 Hz), 7.91 (1H, s).

a2) *trans*-(*E*)-7-Cyano-2-(2-(1-(4-(3-(3-methoxy)phenylpropenoyl)amino)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 444 (MH^+). $C_{28}H_{33}N_3O_2$ requires 443.

^{1}H NMR ($CDCl_3$) δ: 1.00 - 1.40 (5H, m), 1.50 (2H, m), 1.84 (2H, m), 2.05 (2H, m), 2.54 (2H, m), 2.73 (2H, t, J = 6 Hz), 2.95 (2H, t, J = 6 Hz), 3.61 (2H, s), 3.82 (3H, s), 3.85 (1H, m), 5.49 (1H, d, J = 8 Hz), 6.34 (1H, d, J = 16 Hz), 6.89 (1H, dd, J = 8, 2 Hz),

7.01 (1H, m), 7.08 (1H, d, J = 8 Hz), 7.19 (1H, d, J = 8 Hz), 7.28 (2H, m), 7.40 (1H, m), 7.57 (1H, d,J = 15 Hz).

b2) *trans*-(*E*)-2-(2-(1-(4-(3-(3-Acetyl)phenylpropenoyl)amino)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 456 (MH$^+$). $C_{29}H_{33}N_3O_2$ requires 455.

^{1}H NMR ($CDCl_3$) δ: 1.20 (5H, m), 1.51 (2H, m), 1.86 (2H, m), 2.05 (2H, m), 2.54 (2H, m), 2.62 (3H, s), 2.73 (2H, t, J = 6 Hz), 2.93 (2H, t, J = 6 Hz), 3.61 (2H, s), 3.88 (1H, m), 5.51 (1H, d, J = 8 Hz), 6.44 (1H, d, J = 16 Hz), 7.18 (1H, d, J = 8 Hz), 7.32 (1H, s), 7.43 (2H, m), 7.64 (2H, m), 7.91 (1H, d, J = 8 Hz), 8.09 (1H, s).

c2) *trans*-(*E*)-2-(2-(1-(4-(3-(3-Chloro)phenylpropenoyl)amino)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 448 (MH$^+$). $C_{27}H_{30}{}^{35}ClN_3O$ requires 447.

^{1}H NMR ($CDCl_3$) δ: 1.15 (5H, m), 1.50 (2H, m), 1.85 (2H, m), 2.05 (2H, m), 2.53 (2H, m), 2.73 (2H, t, J = 6 Hz), 2.95 (2H, t, J = 6 Hz), 3.61 (2H, s), 4.10 (1H, m), 5.53 (1H, d, J = 8 Hz), 6.36 (1H, d, J = 16 Hz), 7.18 (1H, d, J = 8 Hz), 7.35 (5H, m), 7.48 (1H, s), 7.54 (1H, d, J = 16 Hz).

d2) *trans*-(*E*)-7-Cyano-2-(2-(1-(4-(3-(3-thienyl)propenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 420 (MH$^+$). $C_{25}H_{29}N_3OS$ requires 419.

^{1}H NMR ($CDCl_3$) δ: 1.15 (5H, m), 1.50 (2H, m), 1.84 (2H, m), 2.05 (2H, m), 2.53 (2H, m), 2.72 (2H, t, J = 6 Hz), 2.95 (2H, t, J = 6 Hz), 3.61 (2H, s), 4.12 (1H, m), 5.47 (1H, d, J = 8 Hz), 6.19 (1H, d, J = 16 Hz), 7.19 (1H, d, J = 6 Hz), 7.28 (3H, m), 7.36 (2H, m), 7.59 (1H, d, J = 16 Hz).

e2) *trans*-(*E*)-2-(2-(1-(4-(3-(2-Acetamido)phenylpropenoyl)amino)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 471 (MH$^+$). $C_{29}H_{34}N_4O_2$ requires 470.

^{1}H NMR ($CDCl_3$) δ: 1.00 - 1.40 (5H, m), 1.52 (2H, m), 1.85 (4H, m), 2.04 (2H, m), 2.23 (3H, s), 2.54 (2H, m), 2.74 (2H, m), 2.95 (2H, m), 3.61 (2H, s), 3.82 (1H, m), 5.65 (1H, d, J = 6 Hz), 6.28 (1H, d, J = 16 Hz), 7.21 (2H, m), 7.35 (3H, m), 7.77 (2H, m).

f2) *trans*-2-(2-(1-(4-Benzamido)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 388 (MH$^+$). $C_{25}H_{29}N_3O$ requires 387.

^{1}H NMR ($CDCl_3$) δ: 1.00 - 1.45 (5H, m), 1.55 (2H, m), 1.85 (2H, m), 2.10 (2H, m), 2.55 (2H, m), 2.74 (2H, t, J = 6 Hz), 2.95 (2H, t, J = 6 Hz), 3.61 (2H, s), 4.11 (1H, m), 5.93 (1H, d, J = 8 Hz), 7.19 (1H, d, J = 8 Hz), 7.33 (1H, s), 7.40 (4H, m), 7.75 (2H, m).

g2) *trans*-(*E*)-7-Cyano-2-(2-(1-(4-(3-(2-naphthyl)propenoyl)amino)cyclohexyl)-ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 464 (MH$^+$). $C_{31}H_{33}N_3O$ requires 463.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.40 (5H, m), 1.50 (2H, m), 1.86 (2H, m), 2.08 (2H, m), 2.54 (2H, m), 2.74 (2H, t, J = 6 Hz), 2.94 (2H, t, J = 6 Hz), 3.62 (2H, s), 3.91 (1H, m), 5.51 (1H, d, J = 8 Hz), 6.47 (1H, d, J = 16 Hz), 7.18 (1H, d, J = 8 Hz), 7.32 (1H, s), 7.40 (1H, d, J = 8 Hz), 7.50 (2H, m), 7.36 (1H, d, J = 8 Hz), 7.80 (5H, m).

h2) *trans*-6-Cyano-2-(2-(1-(4-(2-indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 427 (MH$^+$). $C_{27}H_{30}N_4O$ requires 426.

^{1}H NMR (DMSO-d_6) δ: 0.88 (2H, m), 1.03 - 1.32 (5H, m), 1.60 (4H, m), 2.29 (2H, m), 2.46 (2H, m), 2.65 (2H, m), 3.42 (2H, m), 3.56 (1H, m), 6.82 (1H, m), 6.95 (2H, m), 7.09 (1H, d, J = 8 Hz), 7.23 (1H, d, J = 8 Hz), 7.38 (3H, m), 8.01 (1H, d, J = 8 Hz), 11.34 (1H, s).

i2) *trans*-(*E*)-7-Cyano-2-(2-(1-(4-(3-(2-thienyl)propenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 420 (MH$^+$). $C_{25}H_{29}N_3OS$ requires 419.

^{1}H NMR ($CDCl_3$) δ: 1.04 - 1.44 (5H, m), 1.54 (2H, m), 1.84 (2H, m), 2.06 (2H, m), 2.54 (2H, m), 2.74 (2H, m), 2.94 (2H, m), 3.63 (3H, s), 3.86 (1H, m), 5.38 (1H, d, J = 10 Hz), 6.15 (1H, d, J = 16 Hz), 7.04 (1H, m), 7.20 (2H, m), 7.30 (2H, m), 7.41 (1H, dd, J = 9, 1 Hz), 7.75 (1H, d, J = 16 Hz).

j2) *trans*-2-(2-(1-(4-(2-Benzo[b]thienyl)carboxamido)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 444 (MH$^+$). $C_{27}H_{29}N_3OS$ requires 443.

^{1}H NMR ($CDCl_3$) δ: 1.05 - 1.50 (5H, m), 1.53 (2H, m), 1.85 (2H, m), 2.04 (2H, m), 2.55 (2H, m), 2.75 (2H, m), 2.96 (2H, m), 3.64 (2H, s), 3.95 (1H, m), 5.94 (1H, d, J = 10 Hz), 7.13 - 7.52 (6H, m), 7.84 (2H, m).

k2) *trans*-7-Cyano-2-(2-(1-(4-(6-(pyrrolo[3,2-c]pyridyl)carboxamido)cyclohexyl)-ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 428 (MH^+). $C_{26}H_{29}N_5O$ requires 427.

^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 1.04 - 1.55 (5H, m), 1.56 (2H, m), 1.89 (2H, m), 2.11 (2H, m), 2.59 (2H, m), 2.78 (2H, t, J = 7 Hz), 2.97 (2H, m), 3.65 (2H, s), 3.90 (1H, m), 7.09 (1H, s), 7.25 (1H, d, J = 9 Hz), 7.40 (3H, m), 8.25 (1H, d, J = 6 Hz), 8.86 (1H, s).

l2) *trans*-(*E*)-2-(2-(1-(4-(3-(4-Chloro)phenylpropenoyl)amino)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 448 (MH^+). $C_{27}H_{30}{}^{35}ClN_3O$ requires 447.

^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 1.05 - 1.43 (5H, m), 1.53 (2H, m), 1.83 (2H, m), 2.05 (2H, m), 2.55 (2H, m), 2.75 (2H, t, J = 7 Hz), 2.98 (2H, m), 3.64 (2H, s), 3.84 (1H, m), 6.13 (1H, m), 6.38 (1H, d, J = 16 Hz), 7.24 (1H, d, J = 9 Hz), 7.34 (4H, m), 7.42 (3H, m), 7.55 (1H, d, J = 16 Hz).

m2) *trans*-(*E*)-7-Cyano-2-(2-(1-(4-(3-(3,4-methylenedioxy)phenylpropenoyl)amino)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 458 (MH^+). $C_{28}H_{31}N_3O_3$ requires 457.

^{1}H NMR ($CDCl_3$) δ: 1.04 - 1.42 (5H, m), 1.51 (2H, m), 1.85 (2H, m), 2.09 (2H, m), 2.55 (2H, m), 2.75 (2H, m), 2.96 (2H, m), 3.62 (2H, s), 3.85 (1H, m), 5.50 (1H, d, J = 10 Hz), 5.99 (2H, s), 6.19 (1H, d, J = 16 Hz), 6.79 (1H, d, J = 9 Hz), 6.98 (2H, m), 7.20 (1H, d, J = 9 Hz), 7.34 (1H, s), 7.41 (1H, d, J = 9 Hz), 7.54 (1H, d, J = 16 Hz).

n2) *trans*-(*E*)-7-Cyano-2-(2-(1-(4-(3-(5-(1,2-dihydro-2-oxo)-(3*H*)-indolyl)propenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 469 (MH^+). $C_{29}H_{32}N_4O_2$ requires 468.

^{1}H NMR (DMSO-d_6) δ: 0.90 - 1.38 (5H, m), 1.42 (2H, m), 1.82 (4H, m), 2.47 (2H, m), 2.65 (2H, m), 2.86 (2H, m), 3.45 - 3.71 (5H, m), 6.46 (1H, d, J = 16 Hz), 6.85 (1H, d, J = 10 Hz), 7.25 - 7.47 (3H, m), 7.59 (2H, m), 7.87 (2H, d, J = 9 Hz), 10.61 (1H, s).

o2) *trans*-(*E*)-2-(2-(1-(4-(3-(3-Acetamido)phenylpropenoyl)amino)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 471 (MH$^+$). $C_{29}H_{34}N_4O_2$ requires 470.

^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 1.04 - 1.45 (5H, m), 1.56 (2H, m), 1.85 (2H ,m), 2.06 (2H, m), 2.18 (3H, s), 2.59 (2H, m), 2.81 (2H, m), 2.99 (2H, m), 3.66 (2H, s), 3.80 (1H, m), 6.47 (1H, d, J = 16 Hz), 6.95 (1H, m), 7.15 - 7.60 (7H, m), 7.80 (1H, s), 9.24 (1H, br s).

p2) *trans*-2-(2-(1-(4-(2-Benzo[b]furanyl)carboxamido)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 428 (MH$^+$). $C_{27}H_{29}N_3O_2$ requires 427.

^{1}H NMR ($CDCl_3$) δ: 1.05 - 1.46 (5H, m), 1.55 (2H, m), 1.89 (2H, m), 2.14 (2H, m), 2.57 (2H, m), 2.75 (2H, t, J = 7 Hz), 2.95 (2H, m), 3.63 (2H, s), 2.95 (1H, m), 6.45 (1H, d, J = 10 Hz), 7.20 (1H, d, J = 9 Hz), 7.25 - 7.55 (6H, m), 7.67 (1H, d, J = 9 Hz).

q2) *trans*-(*E*)-2-(2-(1-(4-(3-(4-Acetyl)phenylpropenoyl)amino)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 456 (MH$^+$). $C_{29}H_{33}N_3O_2$ requires 455.

^{1}H NMR (DMSO-d_6) δ: 1.00 - 1.40 (5H, m), 1.50 - 1.60 (2H, m), 1.92 (4H, m), 2.60 (2H, m), 2.69 (3H, s), 2.75 (2H, m), 2.97 (2H, m), 3.66 (2H, s), 3.72 (1H, m), 6.83 (1H, d, J = 16 Hz), 7.40 (1H, d, J = 8 Hz), 7.55 (1H, d, J = 16 Hz), 7.66 (2H, m), 7.95 (2H, d, J = 8 Hz), 8.07 (2H, d, J = 8 Hz), 8.17 (1H, d, J = 8 Hz).

r2) *trans*-(*E*)-7-Cyano-2-(2-(1-(4-(3-(4-methylsulfonyl)phenylpropenoyl)amino)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 492 (MH$^+$). $C_{28}H_{33}N_3O_3S$ requires 491.

^{1}H NMR (DMSO-d_6) δ: 1.00 - 1.40 (5H, m), 1.50 - 1.60 (2H, m), 1.90 (4H, m), 2.60 (2H, m), 2.73 (2H, m), 2.95 (2H, m), 3.32 (3H, s), 3.66 (2H, s), 3.72 (1H, m), 6.84 (1H, d, J = 16 Hz), 7.39 (1H, d, J = 8 Hz), 7.56 (1H, d, J = 16 Hz), 7.66 (2H, m), 7.86 (2H, d, J = 8 Hz), 8.03 (2H, d, J = 8 Hz), 8.19 (1H, d, J = 8 Hz).

s2) *trans*-(*E*)-7-Cyano-2-(2-(1-(4-(3-(4-methoxy)phenylpropenoyl)amino)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 444 (MH$^+$). $C_{28}H_{33}N_3O_2$ requires 443.

^{1}H NMR (DMSO-d_6) δ: 1.00 - 1.30 (5H, m), 1.50 (2H, m), 1.80 (4H, m), 2.60 (2H, m), 2.73 (2H, m), 2.94 (2H, m), 3.62 (2H, s), 3.68 (1H, m), 3.85 (3H, s), 6.51 (1H, d, J = 16

Hz), 7.04 (2H, d, J = 9 Hz), 7.38 (2H, m), 7.56 (2H, d, J = 9 Hz), 7.63 (2H, m) and 7.95 (1H, d, J = 8 Hz).

t2) *trans*-(*E*)-7-Cyano-2-(2-(1-(4-(3-(4-methylaminocarbonyl)phenylpropenoyl)-amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 469 (MH$^+$). $C_{29}H_{34}N_4O_2$ requires 470.

^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ: 1.10 - 1.40 (5H, m), 1.60 (2H, m), 1.93 (4H, m), 2.63 (2H, m), 2.77 (2H, m), 2.90 (3H, s), 2.99 (2H, m), 3.68 (2H, s), 3.73 (1H, m), 6.79 (1H, d, J = 16 Hz), 7.43 (1H, d, J = 8 Hz, 7.48 (1H, d, J = 16 Hz), 7.68 (2H, m), 7.74 (2H, d, J = 8 Hz), 7.97 (2H, d, J = 8 Hz), 8.14 (1H, d, J = 8 Hz), 8.60 (1H, m).

u2) *trans*-7-Cyano-2-(2-(1-(4-(3-quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 439 (MH$^+$). $C_{28}H_{30}N_4O$ requires 438.

^{1}H NMR (DMSO-d_6) δ: 1.10 - 1.30 (3H, m), 1.30 - 1.60 (4H, m), 1.80 - 2.10 (4H, m), 2.60 (2H, m), 2.72 (2H, m), 2.94 (2H, m), 3.63 (2H, s), 3.85 (1H, m), 7.37 (1H, d, J = 8 Hz), 7.62 (2H, m), 7.74 (1H, t, J = 7 Hz), 7.92 (1H, t, J = 7 Hz), 8.14 (2H, m), 8.65 (1H, m), 8.86 (1H, s), 9.31 (1H, d, J = 2 Hz).

v2) *trans*-2-(2-(1-(4-(5-Benzimidazolyl)carboxamido)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 428 (MH$^+$). $C_{26}H_{29}N_5O$ requires 427.

^{1}H NMR (DMSO-d_6) δ: 1.00 - 1.20 (2H, m), 1.30 - 1.60 (5H, m), 1.80 - 2.00 (4H, m), 2.60 (2H, m), 2.73 (2H, m), 2.95 (2H, m), 3.64 (2H, s), 3.84 (1H, m), 7.38 (1H, d, J = 8 Hz), 7.65 (3H, m), 7.79 (1H, dd, J = 8, 1.5 Hz), 8.21 (1H, s), 8.23 (1H, d, J = 9 Hz), 8.37 (1H, s).

w2) *trans*-7-Cyano-2-(2-(1-(4-(2-(3-methyl)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 441 (MH$^+$). $C_{28}H_{32}N_4O$ requires 440.

^{1}H NMR (DMSO-d_6) δ: 1.15 - 1.35 (2H, m), 1.35 - 1.65 (5H, m), 1.96 (2H, m), 2.05 (2H, m), 2.60 (5H, m), 2.81 (2H, m), 3.11 (2H, m), 3.69 (2H, s), 3.88 (1H, m), 7.05 (1H, t, J = 7 Hz), 7.31 (1H, dt, J = 7, 1 Hz), 7.43 (1H, d, J = 8 Hz), 7.54 (1H, d, J = 8 Hz), 7.69 (3H, m), 7.82 (1H, d, J = 8 Hz), 11.20 (1H, s).

x2) *trans*-7-Cyano-2-(2-(1-(4-(5-(2-methyl)benzimidazoyl)carboxamido)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 442 (MH$^+$). $C_{27}H_{31}N_5O$ requires 441.

^{1}H NMR ($CDCl_3$) δ: 1.13 - 1.30 (5H, m), 1.52 (2H, m), 1.88 (2H, m), 2.15 (2H, m), 2.56 (2H, m), 2.62 (3H, s), 2.74 (2H, m), 2.95 (2H, m), 3.61 (2H, s), 3.97 (1H, br s), 6.13 (1H, m), 7.19 (1H, d, J = 8 Hz), 7.26 (1H, s), 7.33 (1H, s), 7.40 (1H, d, J = 8 Hz), 7.68 (2H, br s), 8.06 (1H, s).

y2) *trans*-6-Cyano-2-(2-(1-(4-(5-(2-methyl)benzimidazolyl)carboxamido)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 442 (MH$^+$). $C_{27}H_{31}N_5O$ requires 441.

z2) *trans*-2-(2-(1-(4-(2-(5-Acetyl)indolyl)carboxamido)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 469 (MH$^+$). $C_{29}H_{32}N_4O_2$ requires 468.

^{1}H NMR (DMSO-d_6) δ: 1.10 - 1.30 (2H, m), 1.30 - 1.70 (5H, m), 2.10 (4H, m), 2.55 (2H, m), 2.74 (3H, s), 2.81 (2H, m), 3.01 (2H, m), 3.71 (2H, s), 3.89 (1H, m), 7.43 (2H, m), 7.60 (1H, d, J = 8 Hz), 7.69 (2H, m), 7.93 (1H, dd, J = 2, 8 Hz), 8.49 (2H, m), 12.03 (1H, br s).

a3) *trans*-2-(2-(1-(4-(2-(6-Acetyl)indolyl)carboxamido)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 469 (MH$^+$). $C_{29}H_{32}N_4O_2$ requires 468.

^{1}H NMR ($CDCl_3$): δ: 1.10 - 1.40 (5H, m), 1.55 (2H, m), 1.90 (2H, m), 2.20 (2H, m), 2.55 (2H, m), 2.67 (3H, s), 2.75 (2H, t, J = 6 Hz), 2.96 (2H, t, J = 6 Hz), 3.62 (2H, s), 4.05 (1H, m), 6.13 (1H, d, J = 8 Hz), 6.86 (1H, d, J = 2 Hz), 7.19 (1H, d, J = 8 Hz), 7.33 (1H, s), 7.40 (1H, dd, J = 2, 8 Hz), 7.67 (1H, m), 7.74 (1H, m), 8.13 (1H, s), 10.20 (1H, br s).

b3) *trans*-2-(2-(1-(4-(2-(6-Acetyl)indolyl)carboxamido)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 469 (MH$^+$). $C_{29}H_{32}N_4O_2$ requires 468.

^{1}H NMR (DMSO-d_6) δ: 0.80 - 1.50 (7H, m), 1.78 (4H, m), 2.44 (2H, m), 2.53 (3H, s), 2.58 (2H, t, J = 6 Hz), 2.76 (2H, m), 3.54 (2H, s), 3.69 (1H, m), 6.00 - 8.00 (1H, br s),

7.14 (1H, s), 7.21 (1H, d, J = 8 Hz), 7.40 - 7.70 (4H, m), 7.99 (1H, s), 8.31 (1H, d, J = 8 Hz).

c3) *trans*-7-Cyano-2-(2-(1-(4-(2-(6-methylsulfonyl)indolyl)carboxamido)-cyclohexyl)ethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 505 (MH^+). $C_{28}H_{32}N_4O_3S$ requires 504.

^{1}H NMR (DMSO-d_6) δ: 1.05 - 1.65 (7H, m), 1.90 (4H, m), 2.55 (2H, m), 2.75 (2H, t, J = 6 Hz), 2.97 (2H, t, J = 6 Hz), 3.29 (3H, s), 3.66 (2H, s), 3.86 (1H, m), 7.40 (2H, m), 7.65 (3H, m), 7.96 (1H, d, J = 8 Hz), 8.08 (1H, s), 8.55 (1H, d, J = 8 Hz), 12.32 (1H, br s).

d3) *trans*-7-Cyano-2-(2-(1-(4-(5-(1,2-dihydro-2-oxo)-(3*H*)-indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 443 (MH^+). $C_{27}H_{30}N_4O_2$ requires 442.

^{1}H NMR ($CDCl_3$) δ: 1.13 - 1.31 (5H, m), 1.52 (2H, m), 1.84 (2H, m), 2.19 (2H, m), 2.52 (2H, m), 2.72 (2H, m), 2.95 (2H, m), 3.56 (2H, s), 3.61 (2H, s), 3.90 (1H, m), 5.78 (1H, d, J = 8 Hz), 6.87 (1H, m), 7.18 (1H, m), 7.23 (1H, m), 7.33 (1H, s), 7.40 (1H, m), 7.61 (2H, m).

e3) *trans*-6-Cyano-2-(2-(1-(4-(5-(1,2-dihydro-2-oxo)-(3*H*)-indolyl)-carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 443 (MH^+). $C_{27}H_{30}N_4O_2$ requires 442.

^{1}H NMR (CD_3OD) δ: 1.00 - 1.50 (5H, m), 1.59 (2H, m), 1.78 - 2.12 (4H, m), 2.63 (2H, m), 2.83 (2H, m), 2.98 (2H, m), 3.34 (2H, m), 3.74 (2H, m), 3.86 (1H, m), 4.80 (2H, m), 6.94 (1H, m), 7.28 (1H, m), 7.52 (2H, m), 7.74 (2H, m).

f3) *trans*-6-Cyano-2-(2-(1-(4-(2-(4-methylthio)indolyl)carboxamido)cyclohexyl)-ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 473 (MH^+). $C_{28}H_{32}N_4OS$ requires 472.

^{1}H NMR ($CDCl_3$) δ: 1.09 - 1.35 (5H, m), 1.5 (2H, m), 1.85 (2H, m), 2.09 (2H, m), 2.52 (2H, m), 2.56 (3H, s), 2.72 (2H, m), 2.91 (2H, m), 3.62 (2H, s), 3.94 (1H, m), 6.02 (1H, d, J = 8 Hz), 6.91 (1H, m), 6.97 (1H, m), 7.12 - 7.26 (3H, m), 7.33 (1H, s), 7.36 (1H, m), 9.47 (1H, s).

g3) *trans*-6-Cyano-2-(2-(1-(4-(2-(5-methoxy)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 457 (MH$^+$). $C_{28}H_{32}N_4O_2$ requires 456.

^{1}H NMR (DMSO-d_6) δ: 1.04 (2H, m), 1.22 - 1.55 (5H, m), 1.83 (4H, m), 2.49 (2H, m), 2.60 (2H, m), 2.89 (2H, m), 3.75 (6H, m), 6.82 (1H, dd, J = 9, 2 Hz), 7.03 (2H, m), 7.30 (2H, d, J = 8 Hz), 7.58 (2H ,m), 8.16 (1H, d, J = 8 Hz), 11.37 (1H, br s).

h3) *trans*-6-Cyano-2-(2-(1-(4-(2-(5-methylsulfonyl)indolyl)carboxamido)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 505 (MH$^+$). $C_{28}H_{32}N_4O_3S$ requires 504.

^{1}H NMR (DMSO-d_6) δ: 1.30 (2H, m), 1.47 - 1.76 (5H, m), 2.08 (4H, m), 2.74 (2H, m), 2.89 (2H, m), 3.06 (2H, m), 3.40 (3H, s), 3.84 (2H, s), 3.99 (1H, m), 7.52 (2H, m), 7.82 (4H, m), 8.45 (1H, s), 8.65 (1H, d, J = 8 Hz), 12.34 (1H, br s).

i3) *trans*-(*E*)-6-Cyano-2-(2-(1-(4-(3-(2-indolyl)propenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 453 (MH$^+$). $C_{29}H_{32}N_4O$ requires 452.

^{1}H NMR (DMSO-d_6) δ: 0.80 - 1.13 (5H, m), 1.29 (2H, m), 1.68 (4H, m), 2.32 (2H, m), 2.48 (2H, m), 2.67 (2H, m), 3.43 (2H, s), 3.51 (1H, m), 5.71 (1H, d, J = 13 Hz), 6.56 (1H, s), 6.68 (1H, d, J = 13 Hz), 6.83 (1H, t, J = 7 Hz), 7.00 (1H, t, J = 7 Hz), 7.11 (1H, d, J = 8 Hz), 7.38 (4H, m), 8.31 (1H, d, J = 8 Hz), 12.91 (1H, br s).

j3) *trans*-(*E*)-7-Cyano-2-(2-(1-(4-(3-(2-indolyl)propenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 453 (MH$^+$). $C_{29}H_{32}N_4O$ requires 452.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.39 (5H, m), 1.52 (2H, m), 1.85 (2H, m), 2.10 (2H, m), 2.54 (2H, m), 2.73 (2H, t, J = 6 Hz), 2.95 (2H, m), 3.61 (2H, s), 3.83 (1H, m), 5.56 (2H, m), 6.69 (1H, s), 6.77 (1H, d, J = 13 Hz), 7.06 (1H, t, J = 7 Hz), 7.20 (2H, m), 7.33 (1H, s), 7.43 (2H, m), 7.60 (1H, d, J = 8 Hz), 12.51 (1H, br s).

k3) *trans*-(*E*)-7-Cyano-2-(2-(1-(4-(3-(3-indolyl)propenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 453 (MH$^+$). $C_{29}H_{32}N_4O$ requires 452.

^{1}H NMR (DMSO-d_6) δ: 0.85 - 1.50 (7H, m), 1.80 (4H, m), 2.35 (2H, m), 2.61 (2H, m), 2.84 (2H, m), 3.52 (3H, m), 6.56 (1H, d, J = 16 Hz), 7.13 (2H, m), 7.27 (1H, d, J = 8 Hz), 7.41 (1H, d, J = 8 Hz), 7.52 (3H, m), 7.69 (2H, m), 7.84 (1H, m), 11.50 (1H, br s).

l3) *trans*-2-(2-(1-(4-(2-(7-Acetyl)indolyl)carboxamido)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 469 (MH$^+$). $C_{29}H_{32}N_4O_2$ requires 468.

^{1}H NMR (DMSO-d_6) δ: 0.90 - 1.50 (7H, m), 1.85 (4H, m), 2.46 (2H, m), 2.65 (2H, m), 2.69 (3H, s), 2.87 (2H, m), 3.56 (2H, s), 3.74 (1H, m), 7.22 (1H, d, J = 8 Hz), 7.29 (2H, m), 7.55 (2H, m), 8.00 (2H, m), 8.60 (1H, d, J = 8 Hz), 10.90 (1H, s).

m3) *trans*-7-Cyano-2-(2-1-(4-(3-pyridyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 389 (MH$^+$). $C_{24}H_{28}N_4O$ requires 388.

^{1}H NMR (DMSO-d_6) δ: 0.93 - 1.68 (7H, m), 1.88 (4H, m), 2.53 (2H, m), 2.70 (2H, t, J = 6 Hz), 2.92 (2H, t, J = 6 Hz), 3.61 (2H, s), 4.08 (1H, m), 7.35 (1H, d, J = 8 Hz), 7.55 (3H, m), 8.21 (1H, m), 8.45 (1H, d, J = 8 Hz), 8.73 (1H, m), 9.03 (1H, d, J = 2 Hz).

n3) *trans*-6-Cyano-2-(2-(1-(4-(2-(6-fluoro)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 445 (MH$^+$). $C_{27}H_{29}FN_4O$ requires 444.

^{1}H NMR (DMSO-d_6) δ: 1.08 (2H, m), 1.42 (5H, m), 1.84 (4H, m), 2.50 (2H, m), 2.66 (2H, t, J = 6 Hz), 2.84 (2H, m), 3.61 (2H, s), 3.73 (1H, m), 6.90 (1H, m), 7.15 (2H, m), 7.27 (1H, d, J = 8 Hz), 7.61 (3H, m), 8.21 (1H, d, J = 8 Hz), 11.6 (1H, s).

o3) *trans*-6-Cyano-2-(2-(1-(4-(2-(6-methoxy)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 457 (MH$^+$). $C_{28}H_{32}N_4O_2$ requires 456.

^{1}H NMR (DMSO-d_6) δ: 1.11 (2H, m), 1.37 (5H, m), 1.85 (4H, m), 2.54 (2H, m), 2.69 (2H, t, J = 6 Hz), 2.88 (2H, t, J = 6 Hz), 3.65 (2H, s), 3.80 (3H, s), 3.75 - 3.90 (1H, m), 6.72 (1H, dd, J = 2, 8Hz), 6.94 (1H, d, J = 2 Hz), 7.11 (1H, m), 7.32 (1H, d, J = 8 Hz), 7.49 (1H, d, J = 8 Hz), 7.62 (2H, m), 8.10 (1H, d, J = 8 Hz), 11.35 (1H, s).

p3) *trans*-6-Cyano-2-(2-(1-(4-(2-(6-methyl)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 441 (MH$^+$). $C_{28}H_{32}N_4O$ requires 440.

^{1}H NMR (DMSO-d_6) δ: 1.13 (2H, m), 1.42 (5H, m), 1.90 (4H, m), 2.43 (3H, s), 2.54 (2H, m), 2.70 (2H, t, J = 6 Hz), 2.90 (2H, t, J = 6 Hz), 3.65 (2H, s), 3.80 (1H, m), 6.90 (1H, m), 7.12 (1H, m), 7.25 (1H, s), 7.33 (1H, d, J = 8 Hz), 7.52 (1H, d, J = 8 Hz), 7.63 (2H, m), 8.20 (1H, d, J = 8 Hz), 11.4 (1H, s).

q3) *trans*-2-(2-(1-(4-(2-(7-Acetyl)indolyl)carboxamido)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 469 (MH$^+$). $C_{29}H_{32}N_4O_2$ requires 468.

^{1}H NMR (DMSO-d_6) δ: 1.10 (2H, m), 1.39 (5H, m), 1.87 (4H, m), 2.50 (2H, m), 2.67 (2H, t, J = 6 Hz), 2.71 (3H, s), 2.86 (2H, t, J = 6 Hz), 3.63 (2H, s), 3.77 (1H, m), 7.29 (3H, m), 7.59 (2H, m), 8.00 (2H, m), 8.63 (1H, d, J = 8 Hz), 10.93 (1H, s).

r3) *trans*-7-Cyano-2-(2-(1-(4-(2-(5-cyano)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 452 (MH$^+$). $C_{28}H_{29}N_5O$ requires 451.

^{1}H NMR (DMSO-d_6) δ: 1.10 (2H, m), 1.39 (5H, m), 1.85 (4H, m), 2.51 (2H, m), 2.67 (2H, t, J = 6 Hz), 2.85 (2H, m), 3.65 (2H, s), 3.77 (1H, m), 7.28 (2H, m), 7.53 (4H, m), 8.25 (1H, m), 8.45 (1H, d, J = 8 Hz), 12.14 (1H, s).

s3) *trans*-6-Cyano-2-(2-(1-(4-(2-(5-cyano)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 452 (MH$^+$). $C_{28}H_{29}N_5O$ requires 451.

^{1}H NMR (DMSO-d_6) δ: 1.12 (2H, m), 1.41 (5H, m), 1.89 (4H, m), 2.51 (2H, m), 2.70 (2H, t, J = 6 Hz), 2.92 (2H, m), 3.61 (2H, s), 3.82 (1H, m), 7.35 (2H, m), 7.55 (4H, m), (8.28 (1H, m), 8.47 (1H, d, J = 8 Hz), 12.17 (1H, s).

t3) *trans*-7-Cyano-2-(2-(1-(4-(2-(7-cyano)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 452 (MH$^+$). $C_{28}H_{29}N_5O$ requires 451.

^{1}H NMR (DMSO-d_6) δ: 1.08 (2H, m), 1.36 (5H, m), 1.86 (4H, m), 2.47 (2H, m), 2.65 (2H, t, J = 6 Hz), 2.84 (2H, m), 3.61 (2H, s), 3.74 (1H, m), 7.23 (3H, m), 7.57 (2H, m), 7.71 (1H, d, J = 8 Hz), 8.00 (1H, d, J = 8 Hz), 8.33 (1H, d, J = 8 Hz), 12.28 (1H, s).

u3) *trans*-6-Cyano-2-(2-(1-(4-(2-(7-cyano)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API⁺): Found 452 (MH^+). $C_{28}H_{29}N_5O$ requires 451.

^1H NMR (DMSO-d_6) δ: 1.00 - 1.55 (7 H, m), 1.70 - 2.05 (4H, m), 2.50 (2H, m), 2.68 (2H, t, J = 6 Hz), 2.90 (2H, t, J = 6 Hz), 3.59 (2H, s), 3.76 (1H, m), 7.28 (3H, m), 7.58 (2H, m), 7.73 (1H, d, J = 8 Hz), 8.01 (1H, d, J = 8 Hz), 8.35 (1H, d, J = 8 Hz), 12.24 (1H, s).

v3) *trans*-5-Cyano-2-(2-(1-(4-(2-indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API⁺): Found 427 (MH^+). $C_{27}H_{30}N_4O$ requires 426.

^1H NMR (DMSO-d_6 + TFA) δ: 1.14 (2H, m), 1.39 (3H, m), 1.70 (2H, m), 1.89 (4H, m), 3.00 - 3.55 (5H, m), 3.80 (2H, m), 4.38 (1H, m), 4.70 (1H, m), 7.03 (1H, t, J = 9 Hz), 7.17 (2H, m), 7.37 - 7.64 (4H, m), 7.85 (1H, dd, J = 9, 1 Hz), 8.24 (1H, d, J = 9 Hz), 10.30 (1H, br s), 11.53 (1H, br s).

w3) *trans*-(*E*)-5-Cyano-2-(2-(1-(4-(3-phenylpropenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API⁺): Found 414 (MH^+). $C_{27}H_{31}N_3O$ requires 413.

^1H NMR ($CDCl_3$) δ: 1.03 - 1.42 (5H, m), 1.52 (2H, m), 1.82 (2H, m), 2.07 (2H, m), 2.54 (2H, m), 2.75 (2H, t, J = 7 Hz), 3.05 (2H, m), 3.60 (2H, s), 3.87 (1H, m), 5.55 (1H, d, J = 10 Hz), 6.35 (1H, d, J = 16 Hz), 7.21 (2H, m), 7.33 (3H, m), 7.47 (3H, m), 7.61 (1H, d, J = 16 Hz).

x3) *trans*-7-Cyano-2-(2-(1-(4-(2-(4-methylsulfonyl)indolyl)carboxamido)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API⁺): Found 505 (MH^+). $C_{28}H_{32}N_4O_3S$ requires 504.

^1H NMR ($CDCl_3$) δ: 1.06 - 1.35 (5H, m), 1.48 (2H, m), 1.80 (2H, m), 1.98 (2H, m), 2.50 (2H, m), 2.71 (2H, m), 2.91 (2H, m), 3.10 (3H, s), 3.58 (2H, s), 3.84 (1H, br s), 6.10 (1H, d, J = 8 Hz), 7.18 (1H, d, J = 8 Hz), 7.26 - 7.40 (5H, m), 7.70 (2H, d, J = 8 Hz).

y3) (±)-*trans*-7-Cyano-2-(2-(1-(4-(2-(4-methylsulfinyl)indolyl)carboxamido)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API⁺): Found 489 (MH^+). $C_{28}H_{32}N_4O_2S$ requires 488.

^1H NMR ($CDCl_3$) δ: 1.09 - 1.38 (5H, m), 1.49 - 1.59 (2H, m), 1.69 - 1.96 (2H, m), 2.1 (2H, m), 2.57 (2H, m), 2.75 (2H, s), 2.90 (3H, s), 2.98 (2H, m), 3.60 (2H, m), 3.95 (1H,

m), 6.36 (1H, d, J = 8 Hz), 7.20 (1H, d, J = 8 Hz), 7.25 - 7.50 (4H, m), 7.42 (1H, s), 7.59 (1H, d, J = 8 Hz), 10.14 (1H, s).

z3) *trans*-7-Cyano-2-(2-(1-(4-(4-pyridyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 389 (MH$^+$). $C_{24}H_{28}N_4O$ requires 388.

^{1}H NMR ($CDCl_3$) δ: 1.13 - 1.34 (5H, m), 1.52 (2H, m), 1.85 (2H, m), 2.09 (2H, m), 2.55 (2H, m), 2.74 (2H, t, J = 6 Hz), 2.95 (2H, t, J = 6 Hz), 3.62 (2H, s), 3.87 (1H, m), 6.06 (1H, m), 7.19 (1H, d, J = 8 Hz), 7.34 (1H, d, J = 1 Hz), 7.39 (1H, dd, J = 1, 8 Hz), 7.6 (2H, d, J = 6 Hz), 8.72 (2H, d, J = 6 Hz).

a4) *trans*-7-Cyano-2-(2-(1-(4-(4-quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 439 (MH$^+$). $C_{28}H_{30}N_4O$ requires 438.

^{1}H NMR ($CDCl_3$) δ: 1.18 - 1.32 (5H, m), 1.55 (2H, m), 1.90 (2H, m), 2.20 (2H, m), 2.56 (2H, m), 2.74 (2H, t, J = 6 Hz), 2.96 (2H, t, J = 6 Hz), 3.62 (2H, s), 4.10 (1H, m), 5.88 (1H, d, J = 8 Hz), 7.20 (1H, d, J = 8 Hz), 7.33 (1H, s), 7.40 (2H, m), 7.61 (1H, m), 7.77 (1H, m), 8.15 (2H, m), 8.93 (1H, d, J = 4 Hz).

b4) *trans*-6-Cyano-2-(2-(1-(4-(4-quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 439 (MH$^+$). $C_{28}H_{30}N_4O$ requires 438.

^{1}H NMR ($CDCl_3$) δ: 1.17 - 1.32 (5H, m), 1.55 (2H, m), 1.89 (2H, m), 2.19 (2H, m), 2.56 (2H, m), 2.74 (2H, t, J = 6 Hz), 2.93 (2H, t, J = 6 Hz), 3.66 (2H, s), 4.10 (1H, m), 5.95 (1H, m), 7.13 (1H, d, J = 8 Hz), 7.39 (3H, m), 7.61 (1H, m), 7.76 (1H, m), 8.12 - 8.21 (2H, m), 8.92 (1H, m).

c4) *trans*-(*E*)-6-Cyano-2-(2-(1-(4-(3-(2-fluoro)phenylpropenoyl)amino) cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 432 (MH$^+$). $C_{27}H_{30}FN_3O$ requires 431.

^{1}H NMR ($CDCl_3$) δ: 1.00 - 1.45 (5H, m), 1.50 (2H, m), 1.80 (2H, m), 2.05 (2H, m), 2.55 (2H, m), 2.72 (2H, t, J = 6 Hz), 2.92 (2H, t, J = 6 Hz), 3.61 (2H, s), 3.69 (1H, m), 5.53 (1H, d, J = 8 Hz), 6.50 (1H, d, J = 16 Hz), 7.00 - 7.20 (3H, m), 7.25 - 7.55 (4H, m), 7.66 (1H, d, J = 16 Hz).

d4) *trans*-(*E*)-6-Cyano-2-(2-(1-(4-(3-(2-methoxy)phenylpropenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 444 (MH^+). $C_{28}H_{33}N_3O_2$ requires 443.

^{1}H NMR ($CDCl_3$) δ: 1.05 - 1.40 (5H, m), 1.50 (2H, m), 1.80 (2H, m), 2.05 (2H, m), 2.54 (2H, m), 2.72 (2H, t, J = 6 Hz), 2.92 (2H, t, J = 6 Hz), 3.64 (2H, s), 3.75 - 4.0 (1H, m), 3.87 (3H, s), 5.46 (1H, d, J = 8 Hz), 6.48 (1H, d, J = 16 Hz), 6.91 (2H, m), 7.11 (1H, d, J = 8 Hz), 7.25 - 7.40 (3H, m), 7.45 (1H, dd, J = 8, 2 Hz), 7.83 (1H, d, J = 16 Hz).

e4) *trans*-(*E*)-2-(2-(1-(4-(3-(2-Chloro)phenylpropenoyl)amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 448 (MH^+). $C_{27}H_{30}{}^{35}ClN_3O$ requires 447.

^{1}H NMR ($CDCl_3$) δ: 1.05 - 1.45 (5H, m), 1.50 (2H, m), 1.80 (2H, m), 2.05 (2H, m), 2.54 (2H, m), 2.72 (2H, t, J = 6 Hz), 2.90 (2H, t, J = 6 Hz), 3.64 (2H, s), 3.89 (1H, m), 5.53 (1H, d, J = 8 Hz), 6.36 (1H, d, J = 16 Hz), 7.11 (1H, d, J = 8 Hz), 7.25 (2H, m), 7.40 (3H, m), 7.55 (1H, m), 7.95 (1H, d, J = 16 Hz).

f4) *trans*-(*E*)-6-Cyano-2-(2-(1-(4-(3-(2-methyl)phenylpropenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 428 (MH^+). $C_{28}H_{33}N_3O$ requires 427.

^{1}H NMR ($CDCl_3$) δ: 1.05 - 1.45 (5H, m), 1.53 (2H, m), 1.85 (2H, m), 2.10 (2H, m), 2.43 (3H, s), 2.53 (2H, m), 2.73 (2H, t, J = 6 Hz), 2.92 (2H, t, J = 6 Hz), 3.61 (2H, s), 3.89 (1H, m), 5.48 (1H, d, J = 8 Hz), 6.25 (1H, d, J = 16 Hz), 7.05 - 7.30 (4H, m), 7.38 (2H, m), 7.48 (1H, m), 7.89(1H, d, J = 16 Hz).

g4) *trans*-(*E*)-6-Cyano-2-(2-(1-(4-(3-(3-fluoro)phenylpropenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 432 (MH^+). $C_{27}H_{30}FN_3O$ requires 431.

^{1}H NMR ($CDCl_3$) δ: 1.05 - 1.45 (5H, m), 1.50 (2H, m), 1.81 (2H, m), 2.05 (2H, m), 2.54 (2H, m), 2.73 (2H, t, J = 6 Hz), 2.92 (2H, t, J = 6 Hz), 3.64 (2H, s), 3.87 (1H, m), 5.56 (1H, d, J = 8 Hz), 6.35 (1H, d, J = 16 Hz), 6.95 - 7.45 (7H, m), 7.56 (1H, d, J = 16 Hz).

h4) *trans*-(*E*)-6-Cyano-2-(2-(1-(4-(3-(2,6-difluoro)phenylpropenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 450 (MH^+). $C_{27}H_{29}F_2N_3O$ requires 449.

^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 1.03 - 1.42 (5H, m), 1.53 (2H, m), 1.82 (2H, m), 2.05 (2H, m), 2.55 (2H, m), 2.75 (2H, t, J = 6 Hz), 2.94 (2H, t, J = 6 Hz), 3.66 (2H, s), 3.84 (1H, m), 6.19 (1H, br s), 6.70 (1H, d, J = 16 Hz), 6.93 (2H, t, J = 8 Hz), 7.14 (1H, d, J = 8 Hz), 7.28 (1H, m), 7.40 (2H, m), 7.69 (1H, d, J = 16 Hz).

i4) *trans*-(*E*)-6-Cyano-2-(2-(1-(4-(3-(2,3-methylenedioxy)phenylpropenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 458 (MH^+). $C_{28}H_{31}N_3O_3$ requires 457.

^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 1.02 - 1.42 (5H, m), 1.52 (2H, m), 1.83 (2H, m), 2.02 (2H, m), 2.56 (2H, m), 2.77 (2H, t, J = 6 Hz), 2.94 (2H, t, J = 6 Hz), 3.69 (2H, s), 3.91 (1H, m), 6.14 (2H, s), 6.68 (1H, d, J = 16 Hz), 6.83 (2H, m), 6.93 (1H, m), 7.16 (1H, d, J = 8 Hz), 7.40 (1H, d, J = 8 Hz), 7.44 (1H, s), 7.49 (1H, d, J = 16 Hz).

j4) *trans*-(*E*)-6-Cyano-2-(2-(1-(4-(3-(2,3-difluoro)phenylpropenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 450 (MH^+). $C_{27}H_{29}F_2N_3O$ requires 449.

^{1}H NMR ($CDCl_3$) δ: 1.05 - 1.45 (5H, m), 1.52 (2H, m), 1.80 (2H, m), 2.05 (2H, m), 2.54 (2H, m), 2.73 (2H, t, J = 6 Hz), 2.92 (2H, t, J = 6 Hz), 3.64 (2H, s), 3.87 (1H, m), 5.56 (1H, d, J = 8 Hz), 6.52 (1H, d, J = 16 Hz), 6.95 - 7.30 (4H, m), 7.39 (2H, m), 7.63 (1H, d, J = 16 Hz).

k4) *trans*-2-(2-(1-(4-(4-Quinolinyl)carboxamido)cyclohexyl)ethyl)-6-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 482 (MH^+). $C_{28}H_{30}F_3N_3O$ requires 481.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.43 (5H, m), 1.54 (2H, m), 1.89 (2H, m), 2.20 (2H, m), 2.56 (2H, m), 2.75 (2H, t, J = 6 Hz), 2.95 (2H, m), 3.66 (2H, s), 4.06 (1H, m), 5.88 (1H, d, J = 8 Hz), 7.13 (1H, d, J = 8 Hz), 7.36 (2H, m), 7.41 (1H, m), 7.61 (1H, m), 7.77 (1H, m), 8.17 (2H, m), 8.92 (1H, d, J = 4 Hz).

l4) *trans*-2-(2-(1-(4-(4-Quinolinyl)carboxamido)cyclohexyl)ethyl)-6-trifluoromethoxy)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 498 (MH^+). $C_{28}H_{30}F_3N_3O_2$ requires 497.

^{1}H NMR ($CDCl_3$) δ: 1.09 - 1.37 (5H, m), 1.54 (2H, m), 1.89 (2H, m), 2.20 (2H, m), 2.55 (2H, m), 2.72 (2H, t, J = 6 Hz), 2.92 (2H, m), 3.60 (2H, s), 4.04 (1H, m), 5.87 (1H, d, J = 8 Hz), 7.01 (3H, m), 7.41 (1H, d, J = 4 Hz), 7.61 (1H, m), 7.76 (1H, m), 8.15 (2H, m), 8.93 (1H, d, J = 4 Hz).

m4) *trans*-(*E*)-6-Cyano-2-(2-(1-(4-(3-(3-methylsulfonyloxy)phenylpropenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 508 (MH^+). $C_{28}H_{33}N_3O_4S$ requires 507.

^{1}H NMR ($CDCl_3$) δ: 1.00 - 1.40 (5H, m), 1.52 (2H, m), 1.53 (2H, m), 2.05 (2H, m), 2.55 (2H, m), 2.73 (2H, t, J = 6 Hz), 2.92 (2H, t, J = 6 Hz), 3.17 (3H, s), 3.64 (2H, s), 3.85 (1H, m), 5.75 (1H, m), 6.39 (1H, d, J = 16 Hz), 7.12 (1H, d, J = 8 Hz), 7.25 (1H, m), 7.4 (5H, m), 7.56 (1H, d, J = 16 Hz).

n4) *trans*-(*E*)-2-(2-(1-(4-(3-(7-Benzo[b]furanyl)propenoyl)amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 454 (MH^+). $C_{29}H_{31}N_3O_2$ requires 453.

^{1}H NMR ($CDCl_3$) δ: 1.09 - 1.30 (5H, m), 1.51 (2H, m), 1.85 (2H, m), 2.09 (2H, m), 2.55 (2H, m), 2.73 (2H, t, J = 6 Hz), 2.92 (2H, m), 3.65 (2H, s), 3.90 (1H, m), 5.52 (1H, d, J = 8 Hz), 6.82 (1H, d, J = 2 Hz), 7.00 (1H, d, J = 16 Hz), 7.11 (1H, d, J = 8 Hz), 7.26 (1H, m), 7.39 (3H, m), 7.59 (1H, dd, J = 8, 2 Hz), 7.69 (1H, d, J = 2 Hz), 7.76 (1H, d, J = 16 Hz).

o4) *trans*-6-Cyano-2-(2-(1-(4-(4-(6-methoxy)quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 469 (MH^+). $C_{29}H_{32}N_4O_2$ requires 468.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.40 (5H, m), 1.50 - 1.60 (2H, m), 1.80 - 1.90 (2H, m), 2.10 - 2.20 (2H, m), 2.56 (2H, t, J = 8 Hz), 2.74 (2H, t, J = 6 Hz), 2.93 (2H, t, J = 6 Hz), 3.65

(2H, s), 3.93 (3H, s), 4.00 - 4.10 (1H, m), 5.95 (1H, d, J = 8 Hz), 7.10 (1H, d, J = 8 Hz), 7.30 - 7.40 (4H, m), 7.50 (1H, d, J = 2.5 Hz), 8.00 (1H, d, J = 5 Hz), 8.75 (1H, d, J = 5 Hz).

p4) *trans*-(*E*)-6-Cyano-2-(2-(1-(4-(3-(1-naphthyl)propenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoqinoline

Mass spectrum (API$^+$): Found 464 (MH^+). $C_{31}H_{33}N_3O$ requires 463.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.45 (5H, m), 1.53 (2H, m), 1.85 (2H, m), 2.07 (2H, m), 2.55 (2H, m), 2.75 (2H, t, J = 6 Hz), 2.93 (2H, t, J = 6 Hz), 3.65 (2H, s), 3.90 (1H, m), 5.49 (1H, d, J = 8 Hz), 6.42 (1H, d, J = 15 Hz), 7.11 (1H, d, J = 8 Hz), 7.35 - 7.65 (5H, m), 7.67 (1H, d, J = 7 Hz), 7.86 (2H, m), 8.21 (1H, m), 8.43 (1H, d, J = 15 Hz).

q4) *trans*-2-(2-(1-(4-(4-Quinolinyl)carboxamido)cyclohexyl)ethyl)-5-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 482 (MH^+). $C_{28}H_{30}F_3N_3O$ requires 481.

^{1}H NMR (DMSO-d_6) δ: 1.10 - 1.42 (5H, m), 1.50 (2H, m), 1.85 (2H, m), 1.99 (2H, m), 2.52 (2H, m), 2.71 (2H, m), 2.95 (2H, m), 3.65 (2H, s), 3.83 (1H, m), 7.38 (2H, m), 7.54 (2H, m), 7.69 (1H, m), 7.83 (1H, m), 8.11 (2H, m), 8.68 (1H, d, J = 8 Hz), 8.98 (1H, d, J = 4 Hz).

r4) *trans*-(*E*)-2-(2-(1-(4-(3-(3-Cyano)phenylpropenoyl)amino)cyclohexyl)ethyl)-5-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 482 (MH^+). $C_{28}H_{30}F_3N_3O$ requires 481.

^{1}H NMR (DMSO-d_6) δ: 0.99 - 1.37 (5H, m), 1.51 (2H, m), 1.88 (4H, m), 2.56 (2H, m), 2.72 (2H, m), 2.99 (2H, m), 3.68 (3H, m), 6.78 (1H, d, J = 16 Hz), 7.41 (2H, m), 7.51 (1H, d, J = 15 Hz), 7.59 (1H, m), 7.69 (1H, t, J = 8 Hz), 7.90 (2H, m), 8.09 (2H, m).

s4) *trans*-(*E*)-2-(2-(1-(4-(3-Phenylpropenoyl)amino)cyclohexyl)ethyl)-5-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 457 (MH^+). $C_{27}H_{31}F_3N_2O$ requires 456.

^{1}H NMR (DMSO-d_6) δ: 1.00 - 1.34 (5H, m), 1.49 (2H, m), 1.88 (4H, m), 2.52 (2H, m), 2.73 (2H, m), 2.98 (2H, m), 3.67 (3H, m), 6.68 (1H, d, J = 16 Hz), 7.44 (6H, m), 7.60 (3H, m), 8.06 (1H, d, J = 8 Hz).

t4) *trans*-(*E*)-2-(2-(1-(4-(3-(3-Acetamido)phenylpropenoyl)amino)cyclohexyl)ethyl)-5-trifluoromethyl-1,2,3,4-tetrahydrosioquinoline

Mass spectrum (API$^+$): Found 514 (MH$^+$). $C_{29}H_{34}F_3N_3O_2$ requires 513.

^{1}H NMR (DMSO-d_6) δ: 1.00 - 1.30 (5H, m), 1.47 (2H, m), 1.83 (4H, m), 2.08 (3H, s), 2.51 (2H, m), 2.69 (2H, m), 2.94 (2H, m), 3.63 (3H, m), 6.58 (1H, d, J = 16 Hz), 7.22 (1H, m), 7.37 (4H, m), 7.50 (2H, m), 7.95 (1H, m), 8.11 (1H, d, J = 8 Hz), 10.11 (1H, br s).

u4) *trans*-(*E*)-6-Cyano-2-(2-(1-(4-(3-(4-quinolinyl)propenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 465 (MH$^+$). $C_{30}H_{32}N_4O$ requires 464.

^{1}H NMR (DMSO-d_6) δ: 1.00 - 1.35 (5H, m), 1.45 (2H, m), 1.85 (4H, m), 2.54 (2H, m), 2.65 (2H, m), 2.85 (2H, m), 3.60 (2H, s), 3.65 (1H, m), 6.85 (1H, d, J = 16 Hz), 7.30 (1H, d, J = 8 Hz), 7.60 (2H, m), 7.70 (2H, m), 7.85 (1H, m), 8.08 (1H, m), 8.15 (1H, d, J = 16 Hz), 8.25 (2H, m), 8.95 (1H, d, J = 4 Hz).

v4) *trans*-5,6-Difluoro-2-(2-(1-(4-(4-quinolinyl)carboxamido)cyclohexyl)ethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 450 (MH$^+$). $C_{27}H_{29}F_2N_3O$ requires 449.

^{1}H NMR ($CDCl_3$) δ: 1.12 - 1.36 (5H, m), 1.54 (2H, m), 1.89 (2H, m), 2.18 (2H, m), 2.52 (2H, m), 2.69 (2H, t, J = 8 Hz), 2.86 (2H, m), 3.56 (2H, s), 4.05 (1H, m), 5.92 (1H, d, J = 8 Hz), 6.75 (1H, m), 6.93 (1H, m), 7.40 (1H, d, J = 4 Hz), 7.59 (1H, m), 7.75 (1H, m), 8.15 (2H, m), 8.91 (1H, d, J = 4 Hz).

w4) *trans*-(*E*)-5,6-Difluoro-2-(2-(1-(4-(3-phenylpropenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 425 (MH$^+$). $C_{26}H_{30}F_2N_2O$ requires 424.

^{1}H NMR ($CDCl_3$) δ: 1.08 - 1.42 (5H, m), 1.51 (2H, m), 1.81 (2H, m), 2.06 (2H, m), 2.53 (2H, m), 2.71 (2H, m), 2.86 (2H, m), 3.55 (2H, s), 3.89 (1H, m), 5.44 (1H, m), 6.35 (1H, d, J = 16 Hz), 6.75 (1H, m), 6.92 (1H, m), 7.45 (3H, m), 7.49 (2H, m), 7.62 (1H, d, J = 16 Hz).

x4) *trans*-(*E*)-5,6-Difluoro-2-(2-(1-(4-(3-(3-methylsulfonamido)phenylpropenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 518 (MH$^+$). $C_{27}H_{33}F_2N_3O_3S$ requires 517.

^{1}H NMR ($CDCl_3$) δ: 1.05 - 1.38 (5H, m), 1.51 (2H, m), 1.82 (2H, m), 2.05 (2H, m), 2.53 (2H, m), 2.71 (2H, m), 2.88 (2H, m), 3.01 (3H, s), 3.55 (2H, s), 3.93 (1H, m), 5.63 (1H, d, J = 8 Hz), 6.40 (1H, d, J = 16 Hz), 6.74 (1H, m), 6.93 (1H, m), 7.30 (4H, m), 7.48 (1H, s), 7.60 (1H, d, J = 16 Hz).

y4) *trans*-(*E*)-6-Cyano-2-(2-(1-(4-(3-(1-(4-fluoro)naphthyl)propenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 482 (MH^+). $C_{31}H_{32}FN_3O$ requires 481.

^{1}H NMR (DMSO-d_6) δ: 1.05 - 1.45 (5H, m), 1.50 (2H, m), 1.90 (4H, m), 2.55 (2H, m), 2.70 (2H, m), 2.90 (2H, m), 3.66 (2H, s), 3.70 (1H, m), 6.72 (1H, d, J = 16 Hz), 7.35 (1H, d, J = 8 Hz), 7.45 (1H, m), 7.64 (2H, m), 7.81 (3H, m), 8.16 (3H, m), 8.29 (1H, m).

z4) *trans*-(*E*)-2-(2-(1-(4-(3-(4-Benzo[b]furanyl)propenoyl)amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 454 (MH^+). $C_{29}H_{31}N_3O_2$ requires 453.

^{1}H NMR (DMSO-d_6) δ: 1.00 - 1.32 (5H, m), 1.47 (2H, m), 1.85 (4H, m), 2.52 (2H, m), 2.68 (2H, m), 2.86 (2H, m), 3.62 (3H, s), 6.84 (1H, d, J = 16 Hz), 7.34 (3H, m), 7.48 (1H, m), 7.63 (4H, m), 8.07 (1H, m), 8.17 (1H, m).

a5) *trans*-(*E*)-2-(2-(1-(4-(3-(2-Cyano)phenylpropenoyl)amino)cyclohexyl)ethyl)-5-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 482 (MH^+). $C_{28}H_{30}F_3N_3O$ requires 481.

^{1}H NMR ($CDCl_3$) δ: 1.06 - 1.30 (5H, m), 1.52 (2H, m), 1.84 (2H, m), 2.06 (2H, m), 2.53 (2H, m), 2.73 (2H, t, J = 6 Hz), 3.07 (2H, m), 3.66 (2H, s), 3.87 (1H, m), 5.54 (1H, d, J = 8 Hz), 6.66 (1H, d, J = 16 Hz), 7.21 (2H, m), 7.45 (2H, m), 7.61 (2H, m), 7.70 (1H, d, J = 8 Hz), 7.78 (1H, d, J = 16 Hz).

b5) *trans*-(*E*)-2-(2-(1-(4-(3-(4-Cyano)phenylpropenoyl)amino)cyclohexyl)ethyl)-5-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 482 (MH^+). $C_{28}H_{30}F_3N_3O$ requires 481.

^{1}H NMR ($CDCl_3$) δ: 1.08 - 1.30 (5H, m), 1.54 (2H, m), 1.85 (2H, m), 2.06 (2H, m), 2.53 (2H, m), 2.73 (2H, t, J = 6 Hz), 3.07 (2H, m), 3.66 (2H, s), 3.88 (1H, m), 5.54 (1H,d, J = 8 Hz), 6.42 (1H, d, J = 16 Hz), 7.20 (2H, m), 7.47 (1H, m), 7.62 (5H, m).

c5) *trans*-6-Pentafluoroethyl-2-(2-(1-(4-(4-quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 532 (MH$^+$). $C_{29}H_{30}F_5N_3O$ requires 531.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.49 (5H, m), 1.57 (2H, m), 1.91 (2H, m), 2.20 (2H, m), 2.56 (2H, t, J = 7 Hz), 2.75 (2H, t, J = 6 Hz), 2.96 (2H, t, J = 6 Hz), 3.65 (2H, s), 4.05 (1H, m), 5.95 (1H, d, J = 8 Hz), 7.15 (1H, d, J = 8 Hz), 7.33 (2H, m), 7.40 (1H, d, J = 4 Hz), 7.60 (1H, dt, J = 8, 2 Hz), 7.75 (1H, dt, J = 8, 2 Hz), 8.15 (1H, d, J = 8 Hz), 8.21 (1H, d, J = 8 Hz), 8.91 (1H, d, J = 4 Hz).

d5) *trans*-6-Cyano-2-(2-(1-(4-(4-(6-fluoro)quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 457 (MH$^+$). $C_{28}H_{29}FN_4O$ requires 456.

^{1}H NMR ($CDCl_3$) δ: 1.05 - 1.45 (5H, m), 1.55 (2H, m), 1.90 (2H, m), 2.19 (2H, m), 2.56 (2H, m), 2.74 (2H, t, J = 6Hz), 2.93 (2H, t, J = 6Hz), 3.66 (2H, s), 4.04 (1H, m), 5.97 (1H, d, J = 8Hz), 7.11 (1H, d, J = 8Hz), 7.41 (3H, m), 7.52(1H, m), 7.87 (1H, m), 8.12 (lH, m), 8.87 (1H, d, J = 4Hz).

e5) *trans*-6-Cyano-2-(2-(1-(4-(1-isoquinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4 - tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 439 (MH$^+$). $C_{28}H_{30}N_4O$ requires 438.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.45 (5H, m), 1.55 (2H, m), 1.88 (2H, m), 2.16 (2H, m), 2.57 (2H, m), 2.75 (2H, t, J = 6Hz), 2.93 (2H, t, J = 6Hz), 3.66 (2H, s), 3.97 (1H, m), 7.10 (1H, d, J = 8Hz), 7.40 (2H, m), 7.68 (2H, m), 7.83 (2H, m), 8.05 (1H, d, J = 8Hz), 8.45 (1H, d, J = 6Hz), 9.60 (1H, m).

f5) *trans-(E)*-2-(2-(1-(4-(3-(3-Acetamido)phenylpropenoyl)amino)cyclohexyl)-ethyl)-5-pentafluoroethyl-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 564 (MH$^+$). $C_{30}H_{34}F_5N_3O_2$ requires 563.

^{1}H NMR ($CDCl_3$) δ: 1.00 - 1.40 (5H, m), 1.54 (2H, m), 1.83 (2H, m), 2.05 (2H, m), 2.19 (3H, s), 2.54 (2H, m), 2.76 (2H, t, J = 7Hz), 1.97 (2H, m), 3.65 (2 H, s), 3.82 (1H, m), 5.98 (1H, d, J = 8Hz), 6.39 (1H, d, J =16 Hz), 7.19 (2H, m), 7.20 - 7.48 (4H, m) 7.41 (1H, d, J = 8Hz), 7.53 (1H, d, J = 16Hz), 7.80 (1H, br s).

g5) *trans*-6-Cyano-2-(2-(1-(4-(4-(3-fluoro)quinolinyl)carboxamido)-cyclohexyl)ethyl)-1,2,3,4 - tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 457 (MH$^+$)· $C_{28}H_{29}FN_4O$ requires 456.

^{1}H NMR ($CDCl_3$) δ: 1.11 - 1.38 (5H, m), 1.55 (2H, m), 1.89 (2H, m), 2.22 (2H, m), 2.56 (2H, m) 2.74 (2H, t, J = 6Hz), 2.92 (2H, m), 3.65 (2H, s) 4.10 (1H, m), 5.98 (1H, m), 7.11 (1H, d, J = 8Hz), 7.39 (2H, m) 7.67 (2H, m) 8.08 (2H, m), 8.82 (1H, s).

h5) *trans*-6-Cyano-2-(2-(1-(4-(5-isoquinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 439 (MH^+). $C_{28}H_{30}N_4O$ requires 438.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.80 (7H, m), 1.80 - 2.00 (2H, m), 2.10 - 2.30 (2H, m), 2.50 - 2.65 (2H, m), 2.70 - 2.80 (2H, m), 2.85-2.95 (2H, m), 3.66 (2H,s), 3.95 - 4.12 (1H, m), 5.88 (1H, d, J = 8 Hz), 7.12 (1H, d, J = 8Hz), 7.38 -7.45 (2H,m), 7.55 - 7.65 (1H, m), 7.82 (1H, dd, J = 6, 1Hz), 8.04 (1H, d, J = 8 Hz), 8.17 (1H, d, J = 7Hz), 8.58 (1H, d J = 6 Hz), 9.27 (lH, s).

i5) *trans*-6-Cyano-2-(2-(1-(4-(4-(7-fluoro)quinolinyl)carboxamido)cyclohexyl)-ethyl)-1,2,3,4-tetrahydroisoquinoline.

Mass spectrum (API$^+$): Found 457 (MH^+). $C_{28}H_{29}FN_4O$ requires 456.

^{1}H NMR (DMSO-d_6) δ: 1.06 - 1.44 (5H, m), 1.50 (2H, m), 1.88 (2H, m), 2.05 (2H, m), 2.54 (2H, m), 2.72 (2H, t, J = 6Hz), 2.91 (2H, m), 3.68 (2H, s), 3.88 (1H, m), 7.34 (1H, d, J = 8Hz), 7.57 (1H, d, J = 4Hz), 7.71 (3H, m), 7.90 (1H, dd, J = 10, 2Hz), 8.25 (1H, m) 8.76 (1H, d, J = 8Hz), 9.05 (1H, d, J = 4Hz).

j5) *trans*-6-Cyano-2-(2-(1-(4-(5-(1,2-dihydro-2-oxo)quinolinyl)carboxamido)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 455 (MH^+). $C_{28}H_{30}N_4O_2$ requires 454.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.40 (5H, m), 1.55 (2H, m), 1.88 (2H, m), 2.15 (2H, m), 2.55 (2H, m), 2.74 (2H, t, J = 6Hz), 2.92 (2H, t, J = 6Hz), 3.65 (2H, s), 3.98 (1H, m), 6.00 and 6.35 (1H, 2 x d, J = 8Hz), 6.73 (1H, m), 7.11 (1H, d, J = 8Hz), 7.26 (1H, m), 7.40 (3H, m), 7.60 and 7.71 (1H, 2 x s), 7.81 and 8.30 (1H, 2 x d, J = 8Hz), 11.95 and 12.21 (1H, 2 x br s).

k5) *trans*-6-Cyano-2-(2-(1-(4-(5-(2,3-dihydro-3-oxo)-4*H*-benzoxazinyl)-carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 459 (MH^+). $C_{27}H_{30}N_4O_3$ requires 458.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.45 (5H, m), 1.55 (2H, m), 1.87 (2H, m), 2.09 (2H, m), 2.54 (2H, m), 2.73 (2H, t, J = 6Hz), 2.92 (2H t, J = 6Hz), 3.65 (2H, s), 3.90 (1H, m), 4.61

(2H, s), 6.00 (1H, d, J = 8Hz), 6.94 (1H, m), 7.10 (3H, m), 7.40 (2H, m), 10.74 (1H, br s).

l5) *trans*-(*E*)-8-Cyano-2-(2-(1-(4-(3-phenylpropenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 414 (MH$^+$). $C_{27}H_{31}N_3O$ requires 413.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.65 (7H, m), 1.80 - 1.95 (2H, m), 2.08 - 2.15 (2H, m), 2.55 - 2.65 (2H, m), 2.70 - 2.77 (2H, m), 2.89 - 2.95 (2H, m), 3.79 (2H, s), 3.85 - 4.00 (1H, m), 5.39 (1H, d, J = 8Hz), 6.34 (1H, d, J = 16Hz), 7.20 - 7.25 (1H, m), 7.28 - 7.42 (4H, m), 7.43 - 7.54 (3H, m) 7.60 (1H, d, J = 16Hz).

m5) *trans*-8-Cyano-2-(2-(1-(4-(2-indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline.

Mass spectrum (API$^+$): Found 427 (MH$^+$). $C_{27}H_{30}N_4O$ requires 426.

^{1}H NMR ($CDCl_3$) δ: 1.45 - 1.64 (7H, m), 1.80 - 1.95 (2H, m), 2.10 - 2.18 (2H, m), 2.55 - 2.66 (2H, m), 2.70 - 2.80 (2H, m), 2.90 - 2.97 (2H, m), 3.80 (2H, s), 3.90 - 4.00 (1H, m), 5.93 (1H, d, J = 8Hz), 6.79 (1H, m), 7.10 - 7.45 (6H, m), 7.64 (1H, d J = 8Hz), 9.11 (1H, br s).

n5) *trans*-7-Cyano-2-(2-(1-(4-(2-indolyl)carboxamido)cyclohexyl)ethyl)-6-methyl-1,2,3,4-tetrahydroisoquinoline.

Mass spectrum (API$^+$): Found 441 (MH$^+$). $C_{28}H_{32}N_4O$ requires 440.

^{1}H NMR (DMSO-d_6 + TFA) δ: 1.15 (2H, m), 1.40 (3H, m), 1.60 - 2.05 (6H, m), 2.55 (3H, s), 3.15 (2H, m), 3.26 (3H, m), 3.76 (2H, m), 4.32 (1H, m), 4.63 (1H, m), 7.05 (1H, t, J = 8Hz), 7.20 (2H, m), 7.42 (2H, m), 7.61 (1H, d, J = 8Hz), 7.71 (1H, s), 8.25 (1H, d, J = 8Hz), 10.26 (1H, br, s), 11.54 (1H, br s).

o5) *trans*-6-Cyano-2-(2-(1-(4-(2-naphthyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 438 (MH$^+$). $C_{29}H_{31}N_3O$ requires 437.

^{1}H NMR (DMSO-d_6) δ: 1.10 (2H, m), 1.24 - 1.53 (5H, m), 1.88 (4H, m), 2.52 (2H, m), 2.67 (2H, m), 2.86 (2H, m), 3.63 (2H, m), 3.82 (1H, m), 7.30 (1H, d, J = 8 Hz), 7.61 (4H, m), 8.00 (4H, m), 8.42 (2H, m).

p5) *trans*-2-(2-(1-(4-(4-Acetyl)phenyl)benzoyl)aminocyclohexyl)ethyl)-5-cyano-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 506 (MH$^+$). $C_{33}H_{35}N_3O_2$ requires 505.

^{1}H NMR (DMSO-d_6 + TFA) δ: 0.85 - 1.10 (2H, m), 1.12 - 1.40 (3H, m), 1.58 (2H, m), 1.62 - 1.89 (4H, m), 2.50 (3H, m), 3.00 - 3.43 (5H, m), 3.69 (2H, m), 4.25 (1H, m), 4.57 (1H, m), 7.39 (1H, t, J = 9 Hz), 7.48 (1H, d, J = 9 Hz), 7.67 - 7.80 (5H, m), 7.86 (2H, d, J = 9 Hz), 7.95 (2H, d, J = 9 Hz), 8.23 (1H, d, J = 9 Hz), 10.00 (1H, br s).

q5) *trans* -(*E*)-7-Cyano-6-methyl-2-(2-(1-(4-(3-phenylpropenoyl)amino)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

Mass spectrum (API$^+$): Found 428 (MH$^+$). $C_{28}H_{33}N_3O$ requires 427.

^{1}H NMR ($CDCl_3$) δ: 1.05 - 1.43 (5H, m), 1.51 (2H, m), 1.87 (2H, m), 2.08 (2H, m), 2.46 (3H, s), 2.54 (2H, m), 2.71 (2H, t, J = 7Hz), 2.90 (2H, t, J = 7Hz), 3.56 (2H, s), 3.87 (1H, m), 5.51 (1H, d, J = 8Hz), 6.36 (1H, d, J = 16Hz), 7.07 (1H, s), 7.29 (1H, s), 7.35 (3H, m), 7.50 (2H, m), 7.61 (1H, d, J = 16 Hz).

Example 9

***trans*-(*E*)-2-(2-(1-(4-(3-(3-Acetamido)phenylpropenoyl)amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline**

Prepared in a similar manner to Example 3, using (*E*)-3-(3-acetamido)phenylpropenoic acid instead of (*E*)-3-(3-methylsulfonyl)phenylpropenoic acid, in 86% yield.

Mass spectrum (API$^+$): Found 471 (MH$^+$). $C_{29}H_{34}N_4O_2$ requires 470.

^{1}H NMR (DMSO-d_6) δ: 0.88 - 1.17 (5H, m), 1.33 (2H, m), 1.70 (4H, m), 1.96 (3H, s), 2.39 (2H, m), 2.54 (2H, m), 2.74 (2H, m), 3.50 (3H, m), 6.46 (1H, d, J = 16 Hz), 7.09 (1H, m), 7.22 (3H, m), 7.36 (1H, m), 7.48 (2H, m), 7.81 (1H, m), 7.97 (1H, d, J = 8 Hz), 9.97 (1H, br s).

Example 10

***trans*-(*E*)-6-Cyano-2-(2-(1-(4-(3-(3-methoxy)phenylpropenoyl)amino)cyclohexyl)-ethyl)-1,2,3,4-tetrahydroisoquinoline**

Prepared in a similar manner to Example 3, using (*E*)-3-(3-methoxy)phenylpropenoic acid instead of (*E*)-3-(3-methylsulfonyl)phenylpropenoic acid, in 24% yield.

Mass spectrum (API$^+$): Found 444 (MH$^+$). $C_{28}H_{33}N_3O_2$ requires 443.

^{1}H NMR (DMSO-d_6) δ: 0.92 - 1.25 (5H, m), 1.42 (2H, m), 1.79 (4H, m), 2.46 (2H, m), 2.63 (2H, m), 2.83 (2H, m), 3.59 (3H, m), 3.77 (3H, s), 6.59 (1H, d, J = 16 Hz), 6.93 (1H, m), 7.10 (2H, m), 7.32 (3H, m), 7.58 (2H, m), 7.96 (1H, d, J = 8 Hz).

Example 11

***trans*-(*E*)-2-(2-(1-(4-(3-(3-Chloro)phenylpropenoyl)amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline**

Prepared in a similar manner to Example 3, using (*E*)-3-(3-chloro)phenylpropenoic acid instead of (*E*)-3-(3-methylsulfonyl)phenylpropenoic acid, in 72% yield.

Mass spectrum (API$^+$): Found 448 (MH$^+$). $C_{27}H_{30}{}^{35}ClN_3O$ requires 447.

^{1}H NMR (DMSO-d_6) δ: 0.88 - 1.22 (5H, m), 1.39 (2H, m), 1.76 (4H, m), 2.43 (2H, m), 2.59 (2H, m), 2.79 (2H, m), 3.55 (3H, m), 6.60 (1H, d, J = 16 Hz), 7.22 (1H, d, J = 8 Hz), 7.33 (3H, m), 7.50 (4H, m), 7.94 (1H, d, J = 8 Hz).

Example 12

***trans*-2-(2-(1-(4-(4-Cinnolinyl)carboxamido)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline**

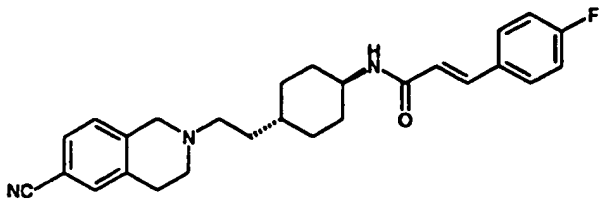
Prepared in a similar manner to Example 7, using cinnoline-4-carboxylic acid instead of 6-cyanoindole-2-carboxylic acid.

Mass spectrum (API$^+$): Found 440 (MH$^+$). $C_{27}H_{29}N_5O$ requires 439.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.50 (5H, m), 1.50 - 1.70 (2H, m), 1.85 (2H, m), 2.25 (2H, m), 2.57 (2H, t, J = 8 Hz), 2.74 (2H, t, J = 6 Hz), 2.96 (2H, t, J = 6 Hz), 3.62 (2H, s), 4.05 (1H, m), 6.08 (1H, br s), 7.20 (1H, d, J = 8 Hz), 7.33 (1H, s), 7.40 (1H, d, J = 8 Hz), 7.80 - 8.00 (2H, m), 8.31 (1H, d, J = 8 Hz), 8.57 (1H, d, J = 8 Hz), 9.28 (1H, s).

Example 13

***trans*-(*E*)-6-Cyano-2-(2-(1-(4-(3-(4-fluoro)phenylpropenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline**



Alternative name: *trans-(E)-N*-[4-[2-(6-Cyano-1,2,3,4-tetrahydroisoquinolin-2-yl)ethyl]cyclohexyl]-3-(4-fluorophenyl)-2-propenamide

Prepared in a similar manner to Example 3, using (*E*)-3-(4-fluoro)phenylpropenoic acid instead of (*E*)-3-(3-methanesulfonyl)phenylpropenoic acid, in 66% yield.

Mass spectrum (API$^+$): Found 432 (MH^+). $C_{27}H_{30}FN_3O$ requires 431.

^{1}H NMR ($CDCl_3$ + CD_3OD) δ: 1.03 - 1.40 (5H, m), 1.54 (2H, m), 1.84 (2H, m), 2.05 (2H, m), 2.55 (2H, m), 2.75 (2H, t, J = 7 Hz), 2.94 (2H, m), 3.66 (2H, s), 3.82 (1H, m), 5.90 - 6.15 (1H, m), 6.30 (1H, d, J = 16 Hz), 6.97 - 7.17 (3H, m), 7.35 - 7.61 (5H, m).

Example 14

***trans*-(*E*)-6-Cyano-2-(2-(1-(4-(3-(2,5-difluoro)phenylpropenoyl)amino)cyclohexyl)-ethyl)-1,2,3,4-tetrahydroisoquinoline**

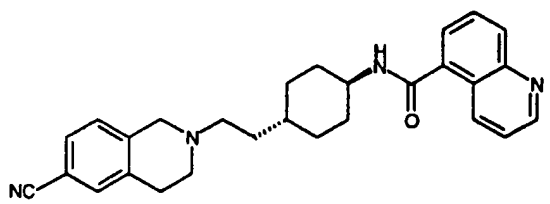
Prepared in a similar manner to Example 3, using (*E*)-3-(2,5-difluoro)phenylpropenoic acid instead of (*E*)-3-(3-methanesulfonyl)phenylpropenoic acid, in 51% yield.

Mass spectrum (API$^-$): Found 448 (MH^-). $C_{27}H_{29}F_2N_3O$ requires 449.

^{1}H NMR ($CDCl_3$) δ: 1.25 (5H, m), 1.53 (2H, m), 1.86 (2H, m), 2.06 (2H, m), 2.55 (2H, m), 2.73 (2H, t, J = 6 Hz), 2.92 (2H, t, J = 6 Hz), 3.65 (2H, s), 3.88 (1H, m), 5.45 (1H, d, J = * Hz), 6.45 (1H, d, J = 16 Hz), 6.90 - 7 20 (4H, m), 7.39 (2H, m), 7.62 (1H, d, J = 16 Hz).

Example 15

***trans*-6-Cyano-2-(2-(1-(4-(5-quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline**



Alternative name: *trans-N*-[4-[2-(6-Cyano-1,2,3,4-tetrahydroisoquinolin-2-yl)ethyl]cyclohexyl]-5-quinolinecarboxamide

Prepared in a similar manner to Example 7, using quinoline-5-carboxylic acid instead of 6-cyanoindole-2-carboxylic acid, in 89% yield.

Mass spectrum (API$^+$): Found 439 (MH$^+$). $C_{28}H_{30}N_4O$ requires 438.

^{1}H NMR ($(CD_3)_2SO$) δ: 1.10 - 1.30 (2H, m), 1.30 - 1.50 (3H, m), 1.50 - 1.60 (2H, m), 1.93 (2H, m), 2.07 (2H, m), 2.60 (2H, m), 2.76 (2H, t, J = 6 Hz), 2.95 (2H, t, J = 6 Hz), 3.72 (2H, s), 3.90 (1H, m), 7.39 (1H, d, J = 8 Hz), 7.60 - 7.70 (3H, m), 7.78 (1H, d, J = 6 Hz), 7.89 (1H, t, J = 7 Hz), 8.20 (1H, d, J = 8 Hz), 8.61 (1H, d, J = 8 Hz), 8.69 (1H, d, J = 8 Hz), 9.05 (1H, m).

Example 16

***trans*-(*E*)-6-Bromo-2-(2-(1-(4-(3-(3-methylsulfonyl)phenylpropenoyl)amino)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline**

Prepared in a similar manner to Example 3, using *trans*-2-(2-(1-(4-amino)cyclohexyl)ethyl)-6-bromo-1,2,3,4-tetrahydroisoquinoline instead of *trans*-2-(2-(1-(4-amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline, in 50% yield.

Mass spectrum (API$^+$): Found 545 (MH$^+$). $C_{27}H_{33}{}^{79}Br_2N_2O_3S$ requires 544.

^{1}H NMR ($CDCl_3$) δ: 1.13 (5H, m), 1.51 (2H, m), 1.82 (2H, m), 2.05 (2H, m), 2.52 (2H, m), 2.69 (2H, t, J = 6 Hz), 2.87 (2H, m), 3.07 (3H, s), 3.54 (2H, s), 3.86 (1H, m), 5.62 (1H, d, J = 8 Hz), 6.49 (1H, d, J = 15 Hz), 6.89 (1H, d, J = 8 Hz), 7.24 (2H, m), 7.63 (3H, m), 7.90 (1H, m), 8.10 (1H, m).

Example 17

***trans*-(*E*)-2-(2-(1-(4-(3-(3-Methylsulfonyl)phenylpropenoyl)amino)-cyclohexyl)ethyl)-6-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline**

Prepared in a similar manner to Example 3, using *trans*-2-(2-(1-(4-amino)cyclohexyl)ethyl)-6-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline instead of *trans*-2-(2-(1-(4-amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline, in 50% yield.

Mass spectrum (API$^+$): Found 535 (MH$^+$). $C_{28}H_{33}F_3N_2O_3S$ requires 534.

^{1}H NMR ($CDCl_3$) δ: 1.17 (5H, m), 1.52 (2H, m), 1.83 (2H, m), 2.06 (2H, m), 2.55 (2H, m), 2.74 (2H, t, J = 6 Hz), 2.95 (2H, m), 3.07 (3H, s), 3.65 (2H, s), 3.86 (1H, m), 5.52 (1H, d, J = 8 Hz), 6.48 (1H, d, J = 15 Hz), 7.12 (1H, d, J = 8 Hz), 7.36 (2H, m), 7.63 (3H, m), 7.90 (1H, m), 8.09 (1H, m).

Example 18

***trans*-(*E*)-2-(2-(1-(4-(3-(3-Methylsulfonyl)phenylpropenoyl)amino)-cyclohexyl)ethyl)-6-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline**

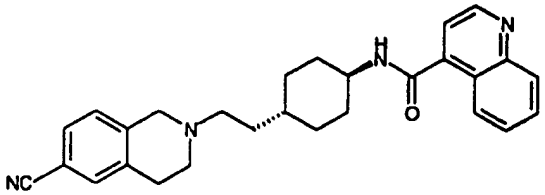
Prepared in a similar manner to Example 3, using *trans*-2-(2-(1-(4-amino)cyclohexyl)ethyl)-6-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline instead of *trans*-2-(2-(1-(4-amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline, in 50% yield.

Mass spectrum (API+): Found 551 (MH^+). $C_{28}H_{33}F_3N_2O_4S$ requires 550.

^1H NMR ($CDCl_3$) δ: 1.15 (5H, m), 1.52 (2H, m), 1.84 (2H, m), 2.06 (2H, m), 2.53 (2H, m), 2.71 (2H, t, J = 6 Hz), 2.91 (2H, m), 3.07 (3H, s), 3.59 (2H, s), 3.85 (1H, m), 5.76 (1H, d, J = 8 Hz), 6.51 (1H, d, J = 15 Hz), 6.99 (3H, m), 7.62 (3H, m), 7.89 (1H, m), 8.10 (1H, m).

Example 19

***trans*-6-Cyano-2-(2-(1-(4-(4-quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline**



Alternative name: *trans*-*N*-[4-[2-(6-cyano-1,2,3,4-tetrahydroisoquinolin-2-yl)ethyl]cyclohexyl]-4-quinolinecarboxamide

A mixture of *trans*-2-(2-(1-(4-amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline (4g, 14.1 mmol), quinoline-4-carboxylic acid (2.45g, 14.1 mmol) 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.71g, 14.1 mmol), 1-hydroxybenzotriazole (0.251g. 1.86 mmol) and dichloromethane (150ml) was stirred at room temperature for 3h. Further dichloromethane (50ml) was added and stirring continued for 17h. Dichloromethane (200ml) was added and the mixture washed with saturated aqueous sodium hydrogen carbonate (500ml). The aqueous phase was extracted with dichloromethane (2x250ml). Combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by chromatography on silica gel (350ml) using 10 - 100% ethyl acetate-hexane then 1-5% methanol-ethyl acetate gradient elution to give the title compound (3.06g, 49.4%) as a colourless solid. A sample recrystallised from ethyl acetate-dichloromethane, m.p. 207 - 210 °C

Mass spectrum (API$^+$): Found 439 (MH$^+$). $C_{28}H_{30}N_4O$ requires 438.

^{1}H NMR ($CDCl_3$) δ: 1.17 - 1.45 (5H, m), 1.53 (2H, m), 1.89 (2H, m), 2.20 (2H, m), 2.55 (2H, m), 2.73 (2H, t, J = 6Hz), 2.91 (2H, t, J = 6Hz), 3.65 (2H, s), 4.07 (1H, m), 5.83 (1H, d, J = 8Hz), 7.10 (1H, d, J = 8Hz), 7.38 (3H, m), 7.60 (1H, m), 7.76 (1H, m), 8.12 (1H, m), 8.19 (1H, m), 8.90 (1H, d, J = 4Hz) : this is a more detailed interpretation of the spectrum for this compound compared to that of Example 8b4..

Treatment of a solution of the free base (1.54 g, 3.52 mmol) in ethanol (10 ml) and dichloromethane (10 ml) with a solution of methanesulfonic acid (0.316 g, 3.3 mmol) in ethanol (2 ml), followed by evaporation *in vacuo*, gave a solid. An aliquot (0.60 g) was recrystallised from 1% aqueous isopropanol to give *trans*-6-cyano-2-(2-(1-(4-(4-quinolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline monomesylate (0.16 g) as an off white solid, m.p. 255 - 259 °C dec.

^{1}H NMR (DMSO-d_6) δ: 1.05 - 1.23 (2H, m), 1.25 - 1.45 (3H, m), 1.69 (2H, m), 1.84 (2H, m), 2.02 (2H, m), 2.30 (3H, s), 3.15 (2H, m), 3.19 - 3.42 (3H, m), 3.65 - 3.95 (2H, m), 4.39 (1H, m), 4.70 (1H, m), 7.45 (1H, d, J = 8 Hz), 7.51 (1H, d, J = 4 Hz), 7.66 (1H, dt, J = 8, 2 Hz), 7.71 - 7.86 (3H, m), 8.09 (2H, m), 8.70 (1H, d, J = 8 Hz), 8.98 (1H, d, J = 4 Hz), 9.84 (1H, br s).

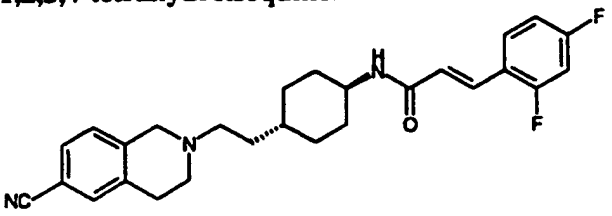
Treatment of a solution of the free base (1.84 g, 4.3 mmol) in methanol (40 ml) and dichloromethane (20 ml) with hydrochloric acid (2M; 2.15 ml), followed by evaporation *in vacuo* gave a solid. Recrystallisation from ethanol (250 ml) gave *trans*-6-cyano-2-(2-(1-(4-(4-quinolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline monohydrochloride (0.86 g) as an off-white solid, m.p. 216 - 219 °C.

Found C, 69.59; H, 6.49; N, 11.61; Cl, 7.47. $C_{28}H_{30}N_4O$. HCl. 0.2 H_2O requires C, 70.33; H, 6.73; N, 11.72; Cl, 7.41%.

^{1}H NMR (DMSO-d_6) δ: 1.03 - 1.25 (2H, m), 1.25 - 1.45 (3H, m), 1.67 - 1.90 (4H, m), 2.01 (2H, m), 3.09 (1H, m), 3.26 (4H, m), 3.72 (1H, m), 3.82 (1H, m), 4.37 (1H, m), 4.65 (1H, m), 7.45 (1H, d, J = 8 Hz), 7.51 (1H, d, J = 4 Hz), 7.64 - 7.87 (4H, m), 8.10 (2H, m), 8.70 (1H, d, J = 8 Hz), 8.97 (1H, d, J = 4 Hz), 11.01 (1H, br s).

Example 20

***trans-(E)*-6-Cyano-2-(2-(1-(4-(3-(2,4-difluoro)phenylpropenoyl)amino)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline.**



Alternative name: *trans-(E)-N*-[4-[2-(6-Cyano-1,2,3,4-tetrahydroisoquinolin-2-yl)ethyl]cyclohexyl]-3-(2, 4-difluorophenyl)-2-propenamide

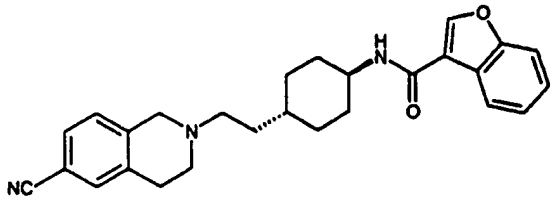
A mixture of *trans*-2-(2-(1-(4-amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline (0.1g, 0.353 mmol), *(E)*-3-(2,4-difluoro)phenylpropenoic acid (0.065 g, 0.353 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.069 g, 0.353 mmol), 1-hydroxybenzotriazole (catalytic amount) and dichloromethane (4ml) was treated in a manner similar to Example 1 to give the title compound (0.131 g, 82%) as a colorless solid.

Mass spectrum (API$^+$): Found 450 (MH^+). $C_{27}H_{29}F_2N_3O$ requires 449.

^{1}H NMR ($CDCl_3$) δ: 1.05 - 1.45 (5H, m), 1.51 (2H, m), 1.80 (2H, m), 2.04 (2H,m), 2.54 (2H, m), 2.73 (2H, t, J = 6Hz), 2.92 (2H, t, J = 6Hz,), 3.64 (2H, s), 3.88 (1H, m), 5.48 (1H, d, J = 8Hz), 6.43 (1H, d, J = 16Hz), 6.86 (2H, m), 7.11 (1H, d, J = 8Hz), 7.42 (3H, m), 7.61 (1H, d, J = 16Hz).

Example 21

***trans*-2-(2-(1-(4-(3-Benzo[b]furanyl)carboxamido)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline**



Alternative name: *trans-N*-[4-[2-(6-cyano-1,2,3,4-tetrahydroisoquinolin-2-yl)ethyl]cyclohexyl]-3-benzofurancarboxamide

A mixture of *trans*-2-(2-(1-(4-amino)cyclohexyl)ethyl-6-cyano-1,2,3,4-tetrahydroisoquinoline (0.1g, 0.353 mmol), benzo[b]furan-3-carboxylic acid (0.052 g, 0.353 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.067 g, 0.353 mmol), 1-hydroxybenzotriazole (catalytic amount) and dichloromethane (4.5 ml ml) was treated in a manner similar to Example 1 to give the title compound (0.076g 51%) as a colourless solid.

Mass spectrum (API$^+$): Found 428 (MH$^+$). $C_{27}H_{29}N_3O_2$ requires 427.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.80 (7H, m), 1.87 (2H, m), 2.15 (2H, m), 2.55 (2H, m), 2.75 (2H, t, J = 5.5Hz), 2.93 (2H, t, J = 5.5 Hz), 3.65 (2H, s), 4.00 (1H, m), 5.83 (1H, d, J = 8Hz), 7.11 (1H, d, J = 8Hz), 7.39 (4H, m), 7.50 (1H, m), 7.87 (1H, m), 8.09 (1H, s).

Example 22

***trans*-6-Cyano-2-(2-(1-(4-(7-indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline**

Prepared in a similar manner to Example 19, using indole-7-carboxylic acid.

Mass spectrum (API$^+$): Found 427 (MH$^+$). $C_{27}H_{30}N_4O$ requires 426.

^{1}H NMR (DMSO-d_6) δ: 1.00 - 1.20 (2H, m), 1.30 - 1.60 (5H, m), 1.80 - 2.00 (4H, m), 2.50 (2H, m), 2.70 (2H, t, J = 5 Hz), 2.90 (2H, t, J = 5 Hz), 3.66 (2H, s), 3.86 (1H, m), 6.53 (1H, t, J = 2 Hz), 7.10 (1H, t, J = 8 Hz), 7.33 (1H, d, J = 8 Hz), 7.39 (1H, t, J = 3 Hz), 7.62 (1H, d, J = 8 Hz), 7.65 (1H, s), 7.69 (1H, d, J = 8 Hz), 7.75 (1H, d, J = 8 Hz), 8.31 (1H, d, J = 8 Hz), 11.19 (1H, s).

Example 23

***trans*-6-Cyano-2-(2-(1-(4-(4-(8-fluoro)quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline**

Prepared in a similar manner to Example 19, using 8-fluoro-quinoline-4-carboxylic acid (prepared according to the methods of McKittrik, *et al.*, J. Het Chem., 1990, **27**(7), 2151; and Senear, *et al.*, J. Amer. Chem. Soc., 1946, **68**, 2695).

Mass spectrum (API$^+$): Found 457 (MH$^+$). $C_{28}H_{29}N_4OF$ requires 456.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.45 (5H, m), 1.65 (2H, m), 1.85 (2H, m), 2.19 (2H, m), 2.56 (2H, m), 2.71 (2H, t, J = 6 Hz), 2.92 (2H, t, J = 6 Hz), 3.65 (2H, s), 4.05 (1H, m), 6.10 (1H, d, J = 8 Hz), 7.11 (1H, d, J = 8 Hz), 7.30 - 7.65 (5H, m), 7.97 (1H, d, J = 8 Hz), 8.95 (1H, d, J = 4 Hz).

Example 24

***trans*-6-Cyano-2-(2-(1-(4-(4-(8-bromo)quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline**

Prepared in a similar manner to Example 19, using 8-bromo-quinoline-4-carboxylic acid (prepared according to the methods of Holt, *et al.*, Proc. Roy. Soc., 1958, **148**, 481; and Senear, *et al.*, J. Amer. Chem. Soc., 1946, **68**, 2695).

Mass spectrum (API$^+$): Found 519 (MH$^+$). $C_{28}H_{29}N_4O^{81}Br$ requires 518.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.45 (5H, m), 1.55 (2H, m), 1.85 (2H, m), 2.20 (2H, m), 2.55 (2H, m), 2.73 (2H, t, J = 6 Hz), 2.91 (2H, t, J = 6 Hz), 3.65 (2H, s), 4.03 (1H, m), 5.85 (1H, d, J = 8 Hz), 7.10 (1H, d, J = 8 Hz), 7.25 - 7.47 (4H, m), 8.10 (1H, dd, J = 8, 2 Hz), 8.20 (1H, dd, J = 8, 2 Hz), 9.05 (1H, d, J = 4 Hz).

Example 25

***trans*-6-Cyano-2-(2-(1-(4-(4-(8-cyano)quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline**

Prepared in a similar manner to Example 19, using 8-cyano-quinoline-4-carboxylic acid (prepared from 8-bromo-quinoline-4-carboxylic acid methyl ester by standard methods).

Mass spectrum (API$^+$): Found 464 (MH^+). $C_{29}H_{29}N_5O$ requires 463.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.45 (5H, m), 1.55 (2H, m), 1.90 (2H, m), 2.19 (2H, m), 2.56 (2H, m), 2.74 (2H, t, J = 6 Hz), 2.92 (2H, t, J = 6 Hz), 3.66 (2H, s), 4.05 (1H, m), 6.10 (1H, d, J = 8 Hz), 7.11 (1H, d, J = 8 Hz), 7.40 (2H, m), 7.55 (1H, h, J = 4 Hz), 7.66 (1H, m), 8.11 (1H, dd, J = 8, 1 Hz), 8.50 (1H, dd, J = 8, 1 Hz), 9.06 (1H, d, J = 4 Hz).

Example 26

***trans*-6-Cyano-2-(2-(1-(4-(5-(8-fluoro)quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline**

Prepared in a similar manner to Example 19, using 8-fluoro-quinoline-5-carboxylic acid (prepared from 3-amino-4-fluorobenzoic acid according to the method of Bradford, *et al.*, J. Chem. Soc., 1947, 437).

Mass spectrum (API$^+$): Found 457 (MH^+). $C_{28}H_{29}N_4OF$ requires 456.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.45 (5H, m), 1.56 (2H, m), 1.89 (2H, m), 2.18 (2H, m), 2.56 (2H, m), 2.73 (2H, t, J = 6 Hz), 2.92 (2H, t, J = 6 Hz), 3.65 (2H, s), 4.05 (1H, m), 5.85 (1H, d, J = 8 Hz), 7.10 (1H, d, J = 8 Hz), 7.35 (3H, m), 7.54 (1H, m), 7.60 (1H, m), 8.85 (1H, d, J = 7 Hz), 9.05 (1H, m).

Example 27

***trans*-6-Cyano-2-(2-(1-(4-(4-(7-cyano)quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline**

Prepared in a similar manner to Example 19, using 7-cyano-quinoline-4-carboxylic acid (prepared from 7-bromo-quinoline-4-carboxylic acid methyl ester by standard methods).

Mass spectrum (API$^+$): Found 464 (MH^+). $C_{29}H_{29}N_5O$ requires 463.

^{1}H NMR (DMSO-d_6) δ: 1.00 - 1.20 (2H, m), 1.20 - 1.40 (3H, m), 1.40 - 1.50 (2H, m), 1.80 - 1.90 (2H, m), 1.90 - 2.00 (2H, m), 2.50 (2H, m), 2.65 (2H, t, J = 8 Hz), 2.84 (2H,

m), 3.61 (2H, s), 3.80 (1H, m), 7.08 (1H, d, J = 8 Hz), 7.56 (1H, d, J = 8 Hz), 7.58 (1H, s), 7.69 (1H, d, J = 4 Hz), 7.97 (1H, dd, J = 9, 2 Hz), 8.27 (1H, d, J = 9 Hz), 8.67 (1H, d, J = 2 Hz), 8.77 (1H, d, J = 8 Hz), 9.12 (1H, d, J = 4 Hz).

Example 28

***trans*-2-(2-(1-(4-(3-(7-Fluoro)benzo[b]furanyl)carboxamido)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline**

Prepared in a similar manner to Example 21, using 7-fluoro-benzo[b]furan-3-carboxylic acid (prepared from 3-bromo-7-fluoro-benzo[b]furan by standard methods).

Mass spectrum (API$^+$): Found 446 (MH$^+$). $C_{27}H_{28}N_3O_2$ requires 445.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.45 (5H, m), 1.55 (2H, m), 1.86 (2H, m), 2.14 (2H, m), 2.56 (2H, m), 2.73 (2H, t, J = 6 Hz), 2.94 (2H, t, J = 6 Hz), 3.65 (2H, s), 3.98 (1H, m), 5.80 (1H, d, J = 8 Hz), 7.10 (2H, m), 7.30 (1H, m), 7.40 (2H, m), 7.67 (1H, d, J = 8 Hz), 8.09 (1H, s).

Example 29

***trans*-2-(2-(1-(4-(3-(5-Cyano)benzo[b]furanyl)carboxamido)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline**

A mixture of *trans*-2-(2-(1-(4-amino)cyclohexyl)ethyl-6-cyano-1,2,3,4-tetrahydroisoquinoline (0.283g, 1.0 mmol), 3-bromo-5-cyano-benzo[b]furan (0.212g, 1.0 mmol) [prepared from 5-bromo-benzo[b]furan using standard methods], tri-*n*-butylamine (0.26 ml) and *trans-bis*-triphenylphosphinepalladium(II)bromide (0.04g) in dimethylacetamide (5 ml) were heated at 100^{o}C under a CO atmosphere at 30 psi for 18h. After cooling, the mixture was partitioned between water and ethyl acetate and the organic phase dried and evaporated *in vacuo*. The residue was chromatographed (Si gel, eluting with 30-100% EtOAc in hexane) to afford the title compound as an off-white solid (0.085g, 20%).

Mass spectrum (API$^+$): Found 453 (MH$^+$). $C_{28}H_{28}N_4O_2$ requires 452.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.40 (5H, m), 1.52 (2H, m), 1.85 (2H, m), 2.15 (2H, m), 2.55 (2H, m), 2.73 (2H, t, J = 6 Hz), 2.92 (2H, t, J = 6 Hz), 3.65 (2H, s), 3.95 (1H, m), 5.85 (1H, d, J = 8 Hz), 7.11 (2H, m), 7.35 - 7.65 (4H, m), 8.40 (1H, s).

Example 30

***trans*-6-Cyano-2-(2-(1-(4-(4-(3-methoxy)quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline**

Prepared in a similar manner to Example 19, using 3-methoxy-quinoline-4-carboxylic acid.

Mass spectrum (API$^+$): Found 469 (MH$^+$). $C_{29}H_{32}N_4O_2$ requires 468.

^{1}H NMR ($CDCl_3$) δ: 1.12 - 1.41 (5H, m), 1.55 (2H, m), 1.89 (2H, m), 2.22 (2H, m), 2.56 (2H, m), 2.74 (2H, t, J = 6 Hz), 2.92 (2H, m), 3.65 (2H, s), 4.06 (3H, s), 4.10 (1H, m), 5.93 (1H, d, J = 8 Hz), 7.12 (1H, d, J = 8 Hz), 7.39 (2H, m), 7.57 (2H, m), 7.93 (1H, dd, J = 8, 1 Hz), 8.04 (1H, dd, J = 8, 1 Hz), 8.80 (1H, s).

Example 31

***trans*-6-Cyano-2-(2-(1-(4-(5-(8-chloro)quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline**

Prepared in a similar manner to Example 19, using 8-chloro-quinoline-5-carboxylic acid (prepared from 3-amino-4-chlorobenzoic acid according to the method of Bradford, *et al.*, J. Chem. Soc., 1947, 437).

Mass spectrum (API$^+$): Found 473 (MH$^+$). $C_{28}H_{29}N_4O^{35}Cl$ requires 472.

^{1}H NMR ($CDCl_3$) δ: 1.10 - 1.45 (5H, m), 1.55 (2H, m), 1.90 (2H, m), 2.20 (2H, m), 2.58 (2H, m), 2.74 (2H, t, J = 6 Hz), 2.93 (2H, t, J = 6 Hz), 3.66 (2H, s), 4.00 (1H, m), 5.93 (1H, d, J = 8 Hz), 7.11 (1H, d, J = 8 Hz), 7.40 (2H, m), 7.55 (2H, m), 7.83 (1H, d, J = 9 Hz), 8.75 (1H, dd, J = 9, 2 Hz), 9.05 (1H, m).

Example 32

***trans*-6-Cyano-2-(2-(1-(4-(3-pyrrolo[2,3-b]pyridyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline**

Prepared in a similar manner to Example 19, using pyrrolo[2,3-b]pyridine-3-carboxylic acid [M.M. Robison, B.L. Robison, J. Am. Chem. Soc. 1956, **78**, 1247], in 27% yield.

Mass spectrum (API$^-$): Found 426 (M-H)$^-$. $C_{26}H_{29}N_5O$ requires 427.

^{1}H NMR (DMSO-d_6) δ: 0.89 - 1.12 (2H, m), 1.13 - 1.50 (5H, m), 1.60 - 1.90 (4H, m), 2.43 (2H, m), 2.60 (2H, m), 2.77 (2H, m), 3.54 (2H, s), 3.69 (1H, m), 7.09 (1H, dd, J = 8, 5 Hz), 7.23 (1H, d, J = 9 Hz), 7.51 (2H, m), 7.69 (1H, d, J = 9 Hz), 8.09 (1H, d, J = 3 Hz), 8.18 (1H, m), 8.37 (1H, dd, J = 9, 2 Hz), 11.98 (1H, br s).

Example 33

***trans*-2-(2-(4-(3-(7-Cyano)benzo[b]furanyl)carboxamido)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline**

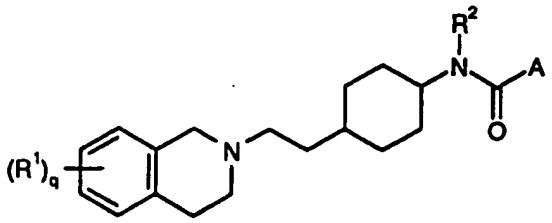
Prepared from 3-bromo-7-cyanobenzo[b]furan (0.318g, 1.5 mmol) [itself prepared from 7-bromobenzo[b]furan using standard methods] using a procedure similar to that of Example 29, in 18% yield.

Mass spectrum (API$^+$): Found 453 (MH^+). $C_{28}H_{28}N_4O_2$ requires 452.

^{1}H NMR ($CDCl_3$) δ: 1.02 - 1.43 (5H, m), 1.54 (2H, m), 1.89 (2H, m), 2.15 (2H, m), 2.56 (2H, t, J = 7 Hz), 2.74 (2H, m), 2.92 (2H, m), 3.65 (2H, s), 3.96 (1H, m), 5.90 (1H, d, J = 9 Hz), 7.15 (1H, d, J = 9 Hz), 7.34 - 7.52 (3H, m), 7.68 (1H, d, J = 9 Hz), 8.17 (1H, s), 8.34 (1H, d, J = 9 Hz).

Claims :

1. A compound of formula (I) :



Formula (I)

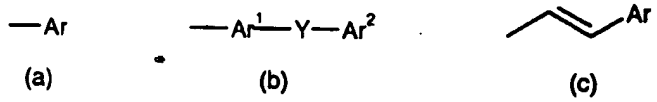
wherein:

R^1 represents a substituent selected from: a hydrogen or halogen atom; a hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethanesulfonyloxy, pentafluoroethyl, C_{1-4}alkyl, C_{1-4}alkoxy, arylC_{1-4}alkoxy, C_{1-4}alkylthio, C_{1-4}alkoxyC_{1-4}alkyl, C_{3-6}cycloalkylC_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkoxycarbonyl, C_{1-4}alkylsulfonyl, C_{1-4}alkylsulfonyloxy, C_{1-4}alkylsulfonylC_{1-4}alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-4}alkyl, C_{1-4}alkylsulfonamido, C_{1-4}alkylamido, C_{1-4}alkylsulfonamidoC_{1-4}alkyl, C_{1-4}alkylamidoC_{1-4}alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-4}alkyl, arylcarboxamidoC_{1-4}alkyl, aroyl, aroylC_{1-4}alkyl, or arylC_{1-4}alkanoyl group; a group $R^3OCO(CH_2)_p$, $R^3CON(R^4)(CH_2)_p$, $R^3R^4NCO(CH_2)_p$ or $R^3R^4NSO_2(CH_2)_p$ where each of R^3 and R^4 independently represents a hydrogen atom or a C_{1-4}alkyl group or R^3R^4 forms part of a C_{3-6}azacyloalkane or C_{3-6}(2-oxo)azacycloalkane ring and p represents zero or an integer from 1 to 4; or a group Ar^3-Z, wherein Ar^3 represents an optionally substituted phenyl ring or an optionally substituted 5- or 6- membered aromatic heterocyclic ring and Z represents a bond, O, S , or CH_2;

R^2 represents a hydrogen atom or a C_{1-4}alkyl group;

q is 1 or 2;

A represents a group of the formula (a), (b) or (c):



(a) (b) (c)

wherein

Ar represents an optionally substituted phenyl ring or an optionally substituted 5- or 6- membered aromatic heterocyclic ring; or an optionally substituted bicyclic ring system;

Ar^1 and Ar^2 each independently represent an optionally substituted phenyl ring or an optionally substituted 5- or 6- membered aromatic heterocyclic ring; and

Y represents a bond, -NHCO-, -CONH-, $-CH_2-$, or $-(CH_2)_mY^1(CH_2)_n-$, wherein Y^1 represents O, S, SO_2, or CO and m and n each represent zero or 1 such that the sum

of m+n is zero or 1; providing that when A represents a group of formula (a), any substituent present in Ar *ortho* to the carboxamide moiety is necessarily a hydrogen or a methoxy group;
and salts thereof.

2. A compound according to claim 1 wherein q represents 1.

3. A compound according to claim 1 or claim 2 wherein A is a group of formula (a) and Ar represents an optionally substituted indolyl, pyrazolo[1,5-a]pyrimidyl, cinnolinyl, quinolinyl, benzo[b]furanyl, or pyrrolopyridyl group.

4. A compound according to claim 1 or claim 2 wherein A is a group of formula (c) and Ar represents an optionally substituted phenyl group.

5. A compound according to any of the preceding claims wherein rings Ar, Ar^1, or Ar^2 are each independently optionally substituted by one or more substituents selected from: a hydrogen or halogen atom, cyano, methoxy, methylenedioxy, acetyl, acetylamino, methylsulfonyl, methylsulfonyloxy, methylaminosulfonyl, methylsulfonylamino, or methylaminocarbonyl group.

6. A compound of formula (I) which is:
trans-7-Cyano-2-(2-(1-(4-(2-indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline
(*E*)-*trans*-7-Cyano-2-(2-(1-(4-(3-(6-indolyl)propenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline
trans-(*E*)-6-Cyano-2-(2-(1-(4-(3-(3-methylsulfonyl)phenylpropenoyl) amino)cyclohexyl)ethyl-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-2-(2-(1-(4-(3-(3-Acetyl)phenylpropenoyl)amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(3-(4,6-dimethyl)pyrazolo[1,5-a]pyrimidyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(2-(5-fluoro)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(2-(6-cyano)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(3,4-methylenedioxy)benzamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(2-indolyl)-*N*-methyl-carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(2-(1-methyl)indolyl)carboxamido)cyclohexyl)ethyl-1,2,3,4-tetrahydroisoquinoline;

trans-7-Cyano-2-(2-(1-(4-(2-(5-nitro)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(2-(5-methylsulfonyl)indolyl)carboxamido) cyclohexyl)-ethyl-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(3-isoquinolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(2-(5-methoxy)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-2-(2-(1-(4-(4-(4-Acetyl)phenyl)benzoyl)aminocyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(2-(7-nitro)indolyl)carboxamido)cyclohexyl)ethyl-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(2-(5-methyl)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(2-(1*H*)-pyrrolo[3,2-b]pyridyl)carboxamido) cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(3-pyrazolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(6-(1-methyl)benzimidazolyl)carboxamido)cyclohexyl)-ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(5-(1,2-dihydro)benzofuranyl)carboxamido)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline
trans-7-Cyano-2-(2-(1-(4-(2-thieno[3,2-b]thiophenyl)carboxamido)cyclohexyl)ethyl-1,2,3,4-tetrahydroisoquinoline
trans-7-Cyano-2-(2-(1-(4-(4-indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline
trans-7-Cyano-2-(2-(1-(4-(2-(6-methoxy)indolyl)carboxamido)cyclohexyl)ethyl-1,2,3,4-tetrahydroisoquinoline
trans-7-Cyano-2-(2-(1-(4-(2-(6-chloro)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline
trans-7-Cyano-2-(2-(1-(4-(2-(6-fluoro)indolyl)carboxamido)cyclohexyl)ethyl-1,2,3,4-tetrahydroisoquinoline
trans-7-Cyano-2-(2-(1-(4-(2-(6-methyl)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline
trans-2-(2-(1-(4-(2-(5-Chloro)benzofuranyl)carboxamido)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline
trans-2-(2-(1-(4-(2-(3-Amino)naphthyl)carboxamido)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline
trans-7-Cyano-2-(2-(1-(4-(2-thienyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline
trans-7-Cyano-2-(2-(1-(4-(2-naphthyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline
trans-7-Cyano-2-(2-(1-(4-(3-indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline

trans-(*E*)-7-Cyano-2-(2-(1-(4-(3-phenylpropenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline
trans-6-Cyano-2-(2-(1-(4-(1-naphthyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-2-(2-(1-(4-(2-Benzo[b]thienyl)carboxamido)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-6-Cyano-2-(2-(1-(4-(5-indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-6-Cyano-2-(2-(1-(4-(6-indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-6-Cyano-2-(2-(1-(4-(2-thieno[3,2-b]thiophenyl)carboxamido)cyclohexyl)-ethyl-1,2,3,4-tetrahydroisoquinoline;
trans-6-Cyano-2-(2-(1-(4-(3,4-methylenedioxy)benzamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-2-(2-(1-(4-(2-Benzofuranyl)carboxamido)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-(E)-6-Cyano-2-(2-(1-(4-(3-(5-(1,2-dihydro-2-oxo)-(3*H*)-indolyl)propenoyl)amino)cyclohexyl)ethyl-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-6-Cyano-2-(2-(1-(4-(3-phenylpropenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-6-Cyano-2-(2-(1-(4-(3-(4-ethylsulfonyl)phenylpropenoyl)-amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-2-(2-(1-(4-(3-(4-Acetyl)phenylpropenoyl)amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-6-Cyano-2-(2-(1-(4-(3-(3,4-methylenedioxy)phenylpropenoyl)-amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-6-Cyano-2-(2-(1-(4-(3-(3-thienyl)propenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-6-Cyano-2-(2-(1-(4-(3-(2-thienyl)propenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-2-(2-(1-(4-(3-(2-Acetyl)phenylpropenoyl)amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-2-(2-(1-(4-(3-(4-Acetyl)phenylpropenoyl)amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-6-Cyano-2-(2-(1-(4-(3-(4-methoxy)phenylpropenoyl)amino)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-2-(2-(1-(4-(3-(4-Chloro)phenylpropenoyl)amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-6-Cyano-2-(2-(1-(4-(3-(3-methylaminocarbonyl)phenylpropenoyl)-amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-6-Cyano-2-(2-(1-(4-(3-(4-methylaminocarbonyl)phenylpropenoyl)-amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(6-indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;

trans-2-(2-(1-(4-(2-(5-Chloro)indolyl)carboxamido)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(3-thienyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-2-(2-(1-(4-(2-(3-Chloro)benzo[b]thienyl)carboxamido)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(6-quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-7-Cyano-2-(2-(1-(4-(3-(2-(3,4-dimethyl)thieno[2,3-b]thiophenyl)propenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-7-Cyano-2-(2-(1-(4-(3-(3-methylaminocarbonyl)phenylpropenoyl)-amino)cyclohexyl)ethyl-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-7-Cyano-2-(2-(1-(4-(3-(3-methoxy)phenylpropenoyl)amino)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-2-(2-(1-(4-(3-(3-Acetyl)phenylpropenoyl)amino)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-2-(2-(1-(4-(3-(3-Chloro)phenylpropenoyl)amino)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-7-Cyano-2-(2-(1-(4-(3-(3-thienyl)propenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-2-(2-(1-(4-(3-(2-Acetamido)phenylpropenoyl)amino)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-2-(2-(1-(4-Benzamido)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-7-Cyano-2-(2-(1-(4-(3-(2-naphthyl)propenoyl)amino)cyclohexyl)-ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-6-Cyano-2-(2-(1-(4-(2-indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-7-Cyano-2-(2-(1-(4-(3-(2-thienyl)propenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-2-(2-(1-(4-(2-Benzo[b]thienyl)carboxamido)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(6-(pyrrolo[3,2-c]pyridyl)carboxamido)cyclohexyl)-ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-2-(2-(1-(4-(3-(4-Chloro)phenylpropenoyl)amino)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-7-Cyano-2-(2-(1-(4-(3-(3,4-methylenedioxy)phenylpropenoyl)amino)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-7-Cyano-2-(2-(1-(4-(3-(5-(1,2-dihydro-2-oxo)-(3*H*)-indolyl)propenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-2-(2-(1-(4-(3-(3-Acetamido)phenylpropenoyl)amino)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-2-(2-(1-(4-(2-Benzo[b]furanyl)carboxamido)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline;

trans-(*E*)-2-(2-(1-(4-(3-(4-Acetyl)phenylpropenoyl)amino)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-7-Cyano-2-(2-(1-(4-(3-(4-methylsulfonyl)phenylpropenoyl)amino)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-7-Cyano-2-(2-(1-(4-(3-(4-methoxy)phenylpropenoyl)amino)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-7-Cyano-2-(2-(1-(4-(3-(4-methylaminocarbonyl)phenylpropenoyl)-amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(3-quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-2-(2-(1-(4-(5-Benzimidazolyl)carboxamido)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(2-(3-methyl)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(5-(2-methyl)benzimidazoyl)carboxamido)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-6-Cyano-2-(2-(1-(4-(5-(2-methyl)benzimidazolyl)carboxamido)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-2-(2-(1-(4-(2-(5-Acetyl)indolyl)carboxamido)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-2-(2-(1-(4-(2-(6-Acetyl)indolyl)carboxamido)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-2-(2-(1-(4-(2-(6-Acetyl)indolyl)carboxamido)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(2-(6-methylsulfonyl)indolyl)carboxamido)-cyclohexyl)ethyl-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(5-(1,2-dihydro-2-oxo)-(3*H*)-indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-6-Cyano-2-(2-(1-(4-(5-(1,2-dihydro-2-oxo)-(3*H*)-indolyl)-carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-6-Cyano-2-(2-(1-(4-(2-(4-methylthio)indolyl)carboxamido)cyclohexyl)-ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-6-Cyano-2-(2-(1-(4-(2-(5-methoxy)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-6-Cyano-2-(2-(1-(4-(2-(5-methylsulfonyl)indolyl)carboxamido)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-6-Cyano-2-(2-(1-(4-(3-(2-indolyl)propenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-7-Cyano-2-(2-(1-(4-(3-(2-indolyl)propenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-7-Cyano-2-(2-(1-(4-(3-(3-indolyl)propenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-2-(2-(1-(4-(2-(7-Acetyl)indolyl)carboxamido)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline;

trans-7-Cyano-2-(2-1-(4-(3-pyridyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-6-Cyano-2-(2-(1-(4-(2-(6-fluoro)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-6-Cyano-2-(2-(1-(4-(2-(6-methoxy)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-6-Cyano-2-(2-(1-(4-(2-(6-methyl)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-2-(2-(1-(4-(2-(7-Acetyl)indolyl)carboxamido)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(2-(5-cyano)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-6-Cyano-2-(2-(1-(4-(2-(5-cyano)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(2-(7-cyano)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-6-Cyano-2-(2-(1-(4-(2-(7-cyano)indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-5-Cyano-2-(2-(1-(4-(2-indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-5-Cyano-2-(2-(1-(4-(3-phenylpropenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(2-(4-methylsulfonyl)indolyl)carboxamido)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
(±)-*trans*-7-Cyano-2-(2-(1-(4-(2-(4-methylsulfinyl)indolyl)carboxamido)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(4-pyridyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(4-quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-6-Cyano-2-(2-(1-(4-(4-quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-6-Cyano-2-(2-(1-(4-(3-(2-fluoro)phenylpropenoyl)amino) cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-6-Cyano-2-(2-(1-(4-(3-(2-methoxy)phenylpropenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-2-(2-(1-(4-(3-(2-Chloro)phenylpropenoyl)amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-6-Cyano-2-(2-(1-(4-(3-(2-methyl)phenylpropenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-6-Cyano-2-(2-(1-(4-(3-(3-fluoro)phenylpropenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;

trans-(*E*)-6-Cyano-2-(2-(1-(4-(3-(2,6-difluoro)phenylpropenoyl)amino) cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-6-Cyano-2-(2-(1-(4-(3-(2,3-methylenedioxy)phenylpropenoyl) amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-6-Cyano-2-(2-(1-(4-(3-(2,3-difluoro)phenylpropenoyl)amino) cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-2-(2-(1-(4-(4-Quinolinyl)carboxamido)cyclohexyl)ethyl)-6-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline;
trans-2-(2-(1-(4-(4-Quinolinyl)carboxamido)cyclohexyl)ethyl)-6-trifluoromethoxy)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-6-Cyano-2-(2-(1-(4-(3-(3-methylsulfonyloxy)phenylpropenoyl) amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-2-(2-(1-(4-(3-(7-Benzo[b]furanyl)propenoyl)amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-6-Cyano-2-(2-(1-(4-(4-(6-methoxy)quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-6-Cyano-2-(2-(1-(4-(3-(1-naphthyl)propenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoqinoline;
trans-2-(2-(1-(4-(4-Quinolinyl)carboxamido)cyclohexyl)ethyl)-5-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-2-(2-(1-(4-(3-(3-Cyano)phenylpropenoyl)amino)cyclohexyl)ethyl)-5-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-2-(2-(1-(4-(3-Phenylpropenoyl)amino)cyclohexyl)ethyl)-5-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-2-(2-(1-(4-(3-(3-Acetamido)phenylpropenoyl)amino)cyclohexyl)ethyl)-5-trifluoromethyl-1,2,3,4-tetrahydrosioquinoline;
trans-(*E*)-6-Cyano-2-(2-(1-(4-(3-(4-quinolinyl)propenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-5,6-Difluoro-2-(2-(1-(4-(4-quinolinyl)carboxamido)cyclohexyl)ethyl-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-5,6-Difluoro-2-(2-(1-(4-(3-phenylpropenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-5,6-Difluoro-2-(2-(1-(4-(3-(3-methylsulfonamido)phenylpropenoyl)amino) cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-6-Cyano-2-(2-(1-(4-(3-(1-(4-fluoro)naphthyl)propenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-2-(2-(1-(4-(3-(4-Benzo[b]furanyl)propenoyl)amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-2-(2-(1-(4-(3-(2-Cyano)phenylpropenoyl)amino)cyclohexyl)ethyl)-5-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-2-(2-(1-(4-(3-(4-Cyano)phenylpropenoyl)amino)cyclohexyl)ethyl)-5-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline;

trans-6-Pentafluoroethyl-2-(2-(1-(4-(4-quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-6-Cyano-2-(2-(1-(4-(4-(6-fluoro)quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-6-Cyano-2-(2-(1-(4-(1-isoquinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4 - tetrahydroisoquinoline;
trans-(*E*)-2-(2-(1-(4-(3-(3-Acetamido)phenylpropenoyl)amino)cyclohexyl)-ethyl)-5-pentafluoroethyl-1,2,3,4-tetrahydroisoquinoline;
trans-6-Cyano-2-(2-(1-(4-(4-(3-fluoro)quinolinyl)carboxamido)-cyclohexyl)ethyl)-1,2,3,4 - tetrahydroisoquinoline;
trans-6-Cyano-2-(2-(1-(4-(5-isoquinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-6-Cyano-2-(2-(1-(4-(4-(7-fluoro)quinolinyl)carboxamido)cyclohexyl)-ethyl)-1,2,3,4-tetrahydroisoquinoline;

trans-6-Cyano-2-(2-(1-(4-(5-(1,2-dihydro-2-oxo)quinolinyl)carboxamido)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-6-Cyano-2-(2-(1-(4-(5-(2,3-dihydro-3-oxo)-4*H*-benzoxazinyl)-carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-8-Cyano-2-(2-(1-(4-(3-phenylpropenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-8-Cyano-2-(2-(1-(4-(2-indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-7-Cyano-2-(2-(1-(4-(2-indolyl)carboxamido)cyclohexyl)ethyl)-6-methyl-1,2,3,4-tetrahydroisoquinoline;
trans-6-Cyano-2-(2-(1-(4-(2-naphthyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans -(*E*)-7-Cyano-6-methyl-2-(2-(1-(4-(3-phenylpropenoyl)amino)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-2-(2-(1-(4-(4-(4-Acetyl)phenyl)benzoyl)aminocyclohexyl)ethyl)-5-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-2-(2-(1-(4-(3-(3-Acetamido)phenylpropenoyl)amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-6-Cyano-2-(2-(1-(4-(3-(3-methoxy)phenylpropenoyl)amino)cyclohexyl)-ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-2-(2-(1-(4-(3-(3-Chloro)phenylpropenoyl)amino)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-2-(2-(1-(4-(4-Cinnolinyl)carboxamido)cyclohexyl)ethyl)-7-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-6-Cyano-2-(2-(1-(4-(3-(4-fluoro)phenylpropenoyl)amino)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-6-Cyano-2-(2-(1-(4-(3-(2,5-difluoro)phenylpropenoyl)amino)cyclohexyl)-ethyl)-1,2,3,4-tetrahydroisoquinoline;

trans-6-Cyano-2-(2-(1-(4-(5-quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-6-Bromo-2-(2-(1-(4-(3-(3-methylsulfonyl)phenylpropenoyl)amino)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-2-(2-(1-(4-(3-(3-Methylsulfonyl)phenylpropenoyl)amino)-cyclohexyl)ethyl)-6-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-2-(2-(1-(4-(3-(3-Methylsulfonyl)phenylpropenoyl)amino)-cyclohexyl)ethyl)-6-trifluoromethoxy-1,2,3,4-tetrahydroisoquinoline;
trans-(*E*)-6-Cyano-2-(2-(1-(4-(3-(2,4-difluoro)phenylpropenoyl)amino)-cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;
trans-2-(2-(1-(4-(3-Benzo[b]furanyl)carboxamido)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-6-Cyano-2-(2-(1-(4-(7-indolyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;

trans-6-Cyano-2-(2-(1-(4-(4-(8-fluoro)quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;

trans-6-Cyano-2-(2-(1-(4-(4-(8-bromo)quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;

trans-6-Cyano-2-(2-(1-(4-(4-(8-cyano)quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;

trans-6-Cyano-2-(2-(1-(4-(5-(8-fluoro)quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;

trans-6-Cyano-2-(2-(1-(4-(4-(7-cyano)quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;

trans-2-(2-(1-(4-(3-(7-Fluoro)benzo[b]furanyl)carboxamido)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-2-(2-(1-(4-(3-(5-Cyano)benzo[b]furanyl)carboxamido)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline;
trans-6-Cyano-2-(2-(1-(4-(4-(3-methoxy)quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;

trans-6-Cyano-2-(2-(1-(4-(5-(8-chloro)quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;

trans-6-Cyano-2-(2-(1-(4-(3-pyrrolo[2,3-b]pyridyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline;

trans-2-(2-(4-(3-(7-Cyano)benzo[b]furanyl)carboxamido)cyclohexyl)ethyl)-6-cyano-1,2,3,4-tetrahydroisoquinoline;

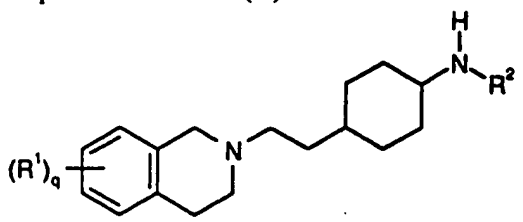
or a salt thereof.

7. *trans*-6-Cyano-2-(2-(1-(4-(4-quinolinyl)carboxamido)cyclohexyl)ethyl)-1,2,3,4-tetrahydroisoquinoline or a salt thereof.

8. A salt according to claim 7 which is the mono hydrochloride or monomesylate salt

9 A process for preparing compounds of formula (I) which process comprises :

(a) reacting a compound of formula(II):



Formula (II)

wherein R^1, R^2, and q are as hereinbefore defined,
with a compound of formula (III):

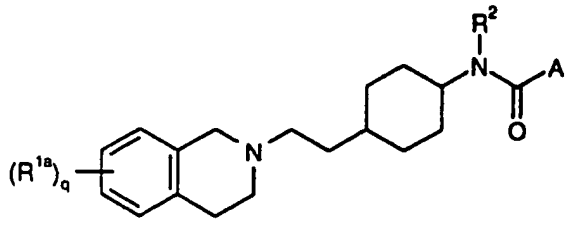
A-COX

Formula (III)

wherein A is as hereinbefore defined and X is a halogen atom or the residue of an activated ester;

(b) to prepare a compound of formula (I) by reacting a compound of formula (II) with a compound A-Br, or A-I, or A-OSO_2CF_3 in the presence of carbon monoxide and a catalyst;

(c) to prepare a compound of formula (I) wherein R^1 is Ar^3-Z and Z is a bond, reacting a compound of formula (IV):

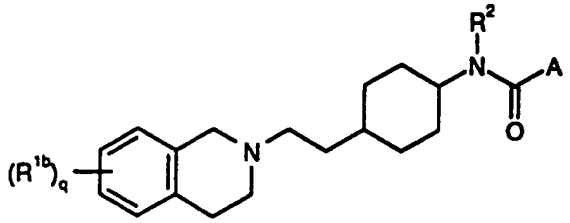


Formula (IV)

wherein A, R^2, and q are as hereinbefore defined, one R^{1a} represents a group W wherein W is a halogen atom or a trifluoromethylsulfonyloxy group, or W is a group M selected

from a boron derivativeor a metal function, and when q is 2 the other R^{1a} is R^1; with a compound Ar^3-W^1, wherein W^1 is a halogen atom or a trifluoromethylsulfonyloxy group when W is a group M or W^1 is a group M when W is a halogen atom or a trifluoromethylsulfonyloxy group;

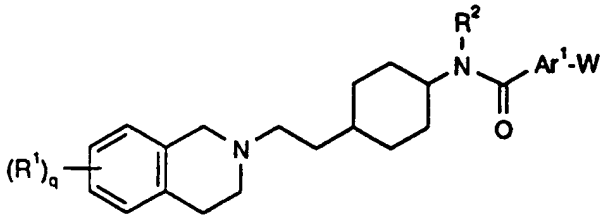
(d) to prepare a compound of formula (I) wherein R^1 is Ar^3-Z and Z is O or S, reacting a compound of formula (V):



Formula (V)

wherein A, R^2, and q are as hereinbefore defined, one R^{1b} represents a group ZH and when q is 2 the other R^{1b} represents R^1; with a reagent serving to introduce the group Ar^3;

(e) to prepare a compound of formula (I) where Y is a bond, reaction of a compound of formula (VI):



Formula (VI)

wherein R^1, R^2, q, Ar^1 and W are as hereinbefore defined, with a compound Ar^2-W^1, wherein W^1 is a halogen atom or a trifluoromethylsulfonyloxy group when W is a group M, or W^1 is a group M when W is a halogen atom or a trifluoromethylsulfonyloxy group.

(f) interconversion of one compound of formula (I) to a different compound of formula (I) e.g. (i) alkylation of a compound (I) wherein R^2 represents hydrogen, (ii) conversion of one R^1 from alkoxy (e.g.methoxy) to hydroxy, or (iii) conversion of R^1 from hydroxy to sulfonyloxy, eg alkylsulfonyloxy or trifluoromethanesulfonyloxy; (iv) conversion of a compound wherein Y represents S to a compound wherein Y is SO_2 or (v) conversion of Y from CO to CH_2;

(g) separation of *cis*- and *trans*- isomers of compounds of formula (I) by conventional methods,;

and optionally thereafter forming a salt of formula (I).

10. A pharmaceutical composition comprising a compound of formula (I) as claimed in any of claims 1 to 7 or a physiologically acceptable salt thereof and a physiologically acceptable carrier therefor.

11. The use of a compound of formula (I) as claimed in any of claims 1 to 7or a physiologically acceptable salt thereof in the manufacture of a medicament for the treatment of a condition which requires modulation of a dopamine receptor.

12. Use acording to claim 11 wherein the dopamine receptor is a dopamine D_3 receptor.

13. Use according to claim 11 or claim 12 wherein a dopamine antagonist is required.

14. Use according to any of claims 11 to 13 wherein the condition is a psychotic condition.

15. Use according to claim 14 wherein the psychotic condition is schizophrenia.

16. A method of treating a condition which requires modulation of a dopamine receptor which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) as claimed in claim 1 or a physiologically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

I. Ional Application No
PCT/EP 98/02583

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D217/04 A61K31/435 C07D401/12 C07D405/12 C07D409/12
C07D413/12 C07D487/04 C07D471/04 C07D495/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 431 580 A (WARNER LAMBERT CO) 12 June 1991 cited in the application see claim 1	1-16
A	US 4 220 778 A (ELLEFSON CHARLES R ET AL) 2 September 1980 see column 5, line 17 - line 22	1-16
A	FR 2 706 895 A (SYNTHELABO) 30 December 1994 see abstract	1-16
P,Y	WO 97 43262 A (SMITHKLINE BEECHAM PLC ;STEMP GEOFFREY (GB); JOHNS AMANDA (GB)) 20 November 1997 see claim 1	1-16

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 September 1998	14/09/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Steendijk, M

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

I. tional Application No
PCT/EP 98/02583

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication.where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 98 06699 A (NASH DAVID JOHN ;STEMP GEOFFREY (GB); SMITHKLINE BEECHAM PLC (GB)) 19 February 1998 see claim 1 -----	1-16

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 98/02583

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